FOOD AND DRUG ADMINISTRATION

+ + + + +

ANTI-INFECTIVE DRUGS ADVISORY COMMITTEE

+ + + + +

62nd MEETING

Thursday, November 20, 1997

Versailles Rooms 3 and 4
Holiday Inn
Bethesda, Maryland

The Committee met, pursuant to notice, at 8:00 a.m., William Craig, M.D., Chair, presiding.

COMMITTEE MEMBERS PRESENT:

WILLIAM CRAIG, M.D. Chair
ERMONA McGOODWIN Exec. Secretary
PARVIN AZIMI, M.D.
VIRGINIA BANKS-BRIGHT, M.D.
GARY CHIKAMI, M.D.
ROBERT DANNER, M.D.
HENRY FRANCIS, M.D.
MARIAN MELISH, M.D.

CARL NORDEN, M.D.
DONALD PARKER, M.D.
KEITH A. RODVOLD, Pharm.D.
JANICE SORETH, M.D.

GUESTS AND CONSULTANTS PRESENT:

SCOTT DOWELL, M.D., M.P.H.
G. SCOTT GIEBINK, M.D.
KENNETH M. GRUNDFAST, M.D.
CHARLES M. MYER, III, M.D.
BARTH RELLER, M.D.
ELLEN R. WALK, M.D.

MEDICAL OFFICERS PRESENT:

ROOPA VIRARAGHAVAN, M.D.
CHERYL McDONALD, M.D.

PRESENTING ON BEHALF OF HOFMANN-LA ROCHE:

JEFFREY BLUMER, M.D.
JEROME KLEIN, M.D.
JONATHAN SOLSKY, M.D.

PRESENTING ON BEHALF OF DAIICHI PHARMACEUTICALS:

GEORGE GATES, M.D.
JEROME KLEIN, M.D.

ELYANE LOMBARDY, M.D.

MINDELL SEIDLIN, M.D.

C O N T E N T S

P R O C E E D I N G S

8:07 a.m.

CHAIRMAN CRAIG: Good morning. I need to announce at the beginning, if any of you are interested in osteoporosis, you are in the wrong room. It's up in the Versailles I and II, and Evista from Eli Lilly is the compound, or raloxifene is being discussed up there. This one is the Anti-Infective Drug Advisory Committee Meeting, the second day of the 62nd meeting of this committee, and the topic on today is ceftriaxone sodium for single dosage of muscular regime of acute otitis media.

What I'd like to do right at the beginning here is to get everybody that's around the tables here, registered on the official record. So I'll start by saying I'm William Craig from the University of Wisconsin, and I'm chair of the advisory committee. And could we start over on my right?

DR. SORETH: I'm Janice Soreth, and I'm a medical team leader in Division of Anti-Infectives.

DR. VIRARAGHAVAN: I'm Roopa Viraraghavan, medical officer, Division of Anti-Infectives.

DR. CHIKAMI: I'm Gary Chikami. I'm the acting division director for the Division of Anti-Infective Drug Products.

DR. BANKS-BRIGHT: Virginia Banks-Bright, Western Reserve Care System, Youngstown, Ohio.

DR. JULIE PARSONNET: I'm Julie Parsonnet from the Divisions of Epidemiology in Infectious Disease at Stanford University.

DR. MELISH: Marian Melish, Pediatric Infectious Disease, University of Hawaii School of Medicine.

DR. PARKER: Don Parker, professor, Department of Statistics and Epidemiology, Oklahoma University Health Science Center.

DR. NORDEN: Carl Norden, Cooper Hospital in Camden, New Jersey, Infectious Disease, and the University of New Jersey in New Brunswick.

DR. RODVOLD: Keith Rodvold, professor at University of Illinois College of Pharmacy in Madison.

MS. McGOODWIN: Ermona McGoodwin, FDA.

DR. AZIMI: Parvin Azimi, Pediatric Infectious Diseases, Children's Hospital, Oakland, California.

DR. DANNER: Robert Danner, National Institutes of Health, Critical Care Medicine Department.

DR. HENRY: Nancy Henry, Pediatric Infectious Diseases, Mayo Clinic, Rochester, Minnesota.

DR. RELLER: Barth Reller, Infectious Diseases and director of Clinical Microbiology, Duke University.

DR. WALD: Ellen Wald, Pediatric Infectious Diseases at the Children's Hospital, Pittsburgh.

DR. GIEBINK: Scott Giebink, Pediatric Infectious Diseases, Pediatrics Otolaryngology, University of Minnesota.

DR. DOWELL: Scott Dowell with the Respiratory Diseases Branch at the Centers for Disease Control and Prevention.

DR. MYER: Charles Myer, Pediatric Otolaryngologist, Children's Hospital, Cincinnati.

CHAIRMAN CRAIG: Thank you, and I'd like again, to extend a welcome to our consultants that are here. And Dr. Grundfast has just arrived if he was -- okay, he has not arrived yet but is one of our other speakers.

As soon as Ermona gets back we'll have her read the Conflict of Interest Statement.

MS. McGOODWIN: Thanks, Dr. Craig. The following announcement addresses the conflict of interest with regard to this meeting and is made a part of the record to preclude even the appearance of such at this meeting.

Based on the submitted agenda and information provided by the participants, the agency has determined that all reported interests in firms regulated by the Center for Drug Evaluation and Research, present no potential for a conflict of interest at this meeting with the following exceptions.

In accordance with Section 208(b)(3), full waivers have been granted to Drs. Rodvold and Danner. Further, Dr. Parvin Azimi has been granted a full waiver that permits her to participate fully in all matters concerning Ofloxacin Otic Solution, and she has been granted a limited waiver and will be permitted to participated in discussions and deliberations relating to Rocephin™ without voting privileges concerning Rocephin™.

A copy of these waiver statements may be obtained by submitting a written request to the agency's Freedom of Information Office, Room 12A30 of the Parklawn Building. With respect to FDA's invited guests, there are reported interests that we believe should be made public to allow the participants to objectively evaluate their comments.

Dr. Scott Dowell owns a nominal amount of stock in American Home Products. Dr. Charles Myer

would like to disclose for the record that he has received honorarium for speaker fees from Daiichi, Abbott, Glaxo-Welcome, and Pharmacia Upjohn. Lastly, Dr. G. Scott Giebink is a consultant to Smith Klein Beechum. Dr. Giebink also reports that in the past he's served as a consultant to Daiichi Pharmaceuticals.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement and their exclusion will be noted for the record.

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

CHAIRMAN CRAIG: Thank you. And this is -- Dr. Grundfast has arrived and should be noted as being present.

Our next speaker is Gary Chikami, acting director for the division that will give some opening remarks.

DR. CHIKAMI: Thank you, Dr. Craig. Since

we have a relatively full schedule today I'll make just a few, brief remarks. Again, I'd like to welcome back the members of our panel and also our consultants for this morning's and this afternoon's sessions.

We'll be changing our focus for this meeting from a general, scientific discussion which occurred yesterday, to product-specific discussions, both of which for today's session, deal with treatment of infections of the ear.

I'd also like, again, to welcome the two pharmaceutical sponsors, Hoffmann-La Roche for this morning's session, and Daiichi Pharmaceuticals for this afternoon's session. I think each of these applications present different issues which the committee will take up as we consider the questions for each of these applications. And I think again, because of the tight schedule I'll stop there and we'll move forward with the Hoffmann-La Roche presentation.

Or, sorry. Actually, we have a presentation from Dr. Giebink.

CHAIRMAN CRAIG: Yes. The next is the background in otitis media that will be presented by Scott Giebink.

DR. GIEBINK: Thank you very much, Dr.

Craig, and it will be a pleasure to stand here and show data published by all of my colleagues sitting around the table here, and I expect helpful criticism as we move along.

I pulled out of a number of slides, this one that I think focuses the concern that many clinicians have today in treating middle ear infections, and that is, the selection of antibiotics in an era of increasing antimicrobial resistance.

Dr. Soreth asked that I begin the discussion by saying a few words about pathogenesis, I believe in an attempt to get most on the panel -- although I heard many infectious disease titles as we went around the table -- and so this will probably be an unnecessary review for many of you.

But as we look at the subject of pathogenesis we know that eustachian tube dysfunction and the invasion of the middle ear by specific bacteria that reside in the nasopharynx, are the two principal events that end up with either acute otitis media or in the absence of these microbes, otitis media with effusion.

Eustachian tube dysfunction, with its either mechanical obstruction or dysfunction of the opening function of the eustachian tube, results in negative

middle ear pressure. Those of you that have gone up or down in altitude or depth in the sea know that Barotrauma also produces negative pressure in the ear with painful consequences leading to serous middle ear transudate.

That alone is called otitis media with effusion, and when organisms invade from the nasopharynx up the eustachian tube and multiply in the middle ear, we end up with acute middle ear inflammation, or otitis media.

Now, focusing just on the events that lead to eustachian tube obstruction, we have the dysfunctional tube. We know that in particular, cleft palate is associated with dysfunction of eustachian tube opening. There are other cranial, facial malformations in young children that have the same effect on the opening function of the tube.

But by far and away the principal factor leading to obstruction is injury of eustachian tube epithelium that's been modeled in animal models, caused by respiratory viruses -- this has been done both with influenza and adenovirus in animal models -- and leading to upstream, if you will, closer to the middle ear secretion of nuclide glycoproteins that then literally plug the eustachian tube.

So that viral, upper respiratory infection is the pathway to eustachian tube obstruction in the vast majority of children who have garden variety, if you will, otitis media. And it's of course, in this realm that daycare plays a principal role as a mechanism for transmitting these respiratory viruses among children.

There are other risk factors such as passive smoke and perhaps respiratory allergy contributing here. And we know that as children grow up, both the length and the angle of the eustachian tube changes with respect to the nasopharynx, probably leading to greater protection of the middle ear from these sorts of events.

Fortunately, there are a relatively few number of respiratory viruses that are the principal bad actors in leading to tubal obstruction. These are principally respiratory syncytial virus which, in all cases, complicated about a third of these infections, by acute otitis media. For the first and second RSV infections in infancy these rates may be as high as 70 or 80 percent.

Adenovirus in influenza and B viruses and to a lesser extent, parainfluenza viruses, are the principal viral precipitators of tubal obstruction

leading to otitis media.

The common cold virus, rhinoviruses, are a relatively small actor in the cause of eustachian tube dysfunction and acute otitis media, representing only a slight boost in AOM complication rates over children that have no respiratory virus infection.

So that when there is a viral URI then, we also know that there's increased bacterial adhesion that complicates the viral adhesion of the viral infection of the nasopharyngeal and eustachian tube epithelium.

That compromises host defenses, permits greater colonization of the nasopharynx with the principal bacteria which cause AOM, and it's of course at this level that we see immune deficiency, whether it's acquired or just delayed maturation of antibody production, contribute to the better or worse state of these defenses in invasion and replication of bacteria in the middle ear.

Now, specific to the discussion this morning, it's important to focus on the bacteria that are the secondary invaders, if you will, in this process. We've recognized now particularly, that there are bacteriologic techniques being used by investigators that allow the recovery of more

fastidious organisms, particularly pneumococci; that approximately 50 percent of AOM disease is caused by the pneumococcus.

Both Dr. Mandel who's here now, and Del Baccario in Seattle, have published relatively recent papers showing the high rate of pneumococcal recovery when more fastidious techniques are used. Haemophilus influenzae -- and these are non-typable organisms without a capsule not affected by the HIB vaccine -- account for about one-in-five of these infections; Moraxella catarrhalis for about one-in-six or seven.

Group A streptococcus, strep phygenes still occasionally causes AOM, a smattering of other organisms, and really in only a very small number of acute effusions is it not possible to grow organisms when all of these middle ear fluids are subjected to molecular methods such as PCR looking for DNA of these organisms.

DNA of these organisms, particularly this, are recovered in virtually 100 percent of these infections. So acute otitis media is a bacterial infection of the middle ear. If I were to overlay viral culture of the nasopharynx and viral acute and convalescent viral serology on top of this, we'd find that half to two-thirds of this pie is overlaid by

respiratory viral infection.

But the respiratory virus alone in the absence of the bacteria, probably only induces a very transient myringitis, if any inflammation of the middle ear at all, absent the bacteria.

Now, one of the more difficult problems facing the clinician, and certainly the parent, not to mention the child, is recurrent acute otitis media. And I illustrate this here because I'm certain the discussion will evolve into an effect of an antibiotic on the later stages of otitis media and recovery of the disease.

I think it's important to think of a detection of disease versus time illustration which I've done here, simply drawing the detection threshold as a horizontal line here, in illustrating three episodes of acute otitis media where there are symptoms and signs of middle ear inflammation that exceed that threshold.

Now, if we are using as a threshold the question, does your ear hurt, that threshold is probably way up here. If we're using computed tomography we're probably down here. The average clinician has a pneumatic otoscope, hopefully, and some have a tympanometer, and are able to detect

otitis media at about this stage.

When we say that the inflammation has resolved, it's resolved with respect to the diagnostic instrument we're using. So that if we set our threshold here at this point we say the ear has healed. Well, it may or may not have dropped back down to the normal state here.

It may have dropped here, it may have dropped here, it may only drop just a shade under line; which is why improved diagnostic techniques are tremendously important in getting at this subclinical, middle ear inflammation that exists in many children who are having recurrent AOM.

When an episode resolves more slowly and passes an arbitrary time point of say, two, three or four months of effusion, we arbitrarily say that child has chronic otitis media with effusion, depending on how flat that resolution slope happens to be. But in fact, if we were able to measure all the way back down to the baseline, I think our concept of otitis media with effusion and ray of healing, would change dramatically.

So all in all, all of the otitis medias that you hear about -- and there are a number of adjectives that are used to describe otitis media -- really

represent one continuous disease, with the vast majority of the disease burden occurring during infancy and early childhood, represented by these acute purulent, middle ear infections, some of these going on to chronic otitis media with effusion.

Most of this disease represented by a secretory transformation -- I'll tell you in just a moment -- of the middle ear epithelium resulting in mucoid secretions. This entity is called by many Europeans, secretory otitis media; in this country tends to be called mucoid otitis media.

Some of the serous transudate that has occurred way back here, persists on in this stage, and some of these children go on and develop chronic, intractable middle ear pathology that is called chronic otitis media. And here we're thinking of granulation tissue in the middle ear, cholesteatoma, damage to the middle ear ossicle, and the like.

Now, I think a picture is worth a thousand words, and I just wanted to show you what the histology of middle ear mucosa looks like during these stages of the disease. This is temporal bone down here. This is just a shade of the cochlea here. This is the middle ear space, the epithelium of the middle ear, the subepithelial space, and the periosteum

overlying the bone. This is normal, middle ear mucosa.

At the same magnification, this is serous otitis media that accompanies eustachian tube obstruction or dysfunction. Here we just barely see the periosteum, the tremendous subepithelial edema. You'll notice how much more spread-apart these fibroblasts are. And virtually no change in the middle ear epithelium. So this is a transudative process that involves capillaries and lymphatic in the subepithelial space.

In acute otitis media which overlays that serous transudative process, we see this abundant infiltration by polymorphonuclear leukocytes in the subepithelial space. Here again is the periosteum down here, dilated vessels, very little change in the epithelium, and neutrophils -- of course, pus in the middle ear space here.

Now for some reason that we're just barely starting to understand from molecular techniques, when this ear undergoes the transition from acute otitis media to mucoid otitis media, there is a phenomenal metaplasia of the lining epithelium of the middle ear.

So that now instead of dealing with squamous and cuboidal epithelial cells, we have this uniform

picture of tall, pseudo-stratified and columnar epithelium, all filled with mucous-like protein the secretory globules out here at the middle ear space surface.

We still see some of this sub-epithelial edema and vascular dilatation, but the process has evolved to a mucoid, secretory process, due to transformation of the epithelium. This is why OME, that takes on this secretory or mucoid characteristic doesn't disappear in a day or two. It doesn't disappear because the epithelium has undergone this transformation.

And this is probably the most difficult concept to explain to parents; that we're not just dealing with a space filled with water or pus; that in fact it's a space filled with water or pus that's lined by a very bioactive membrane, the middle ear epithelium.

Okay, so I'm going to shift gears then, and we'll talk about these bacteria that cause acute otitis media, and focus specifically on the increased, microbial resistance -- and Scott, are you going to be saying more on pneumococcal resistance? If not, you're welcome to ask Scott because he has all this information about pneumococcal resistance from the

CDC.

This is a very simple illustration that demonstrates the increasing beta-lactam resistance among the three major middle ear pathogens -- Moraxella catarrhalis, Haemophilus influenzae, and Strepto pneumoniae -- over the last 25 years. And as you know, Moraxella was the first to demonstrate resistance to beta-lactams due exclusively to production of beta-lactamase, so that we're now dealing in virtually all parts of the country -- and world for that matter -- with Moraxella that are 90-plus percent resistant to beta-lactam drugs due to the production of beta-lactamase.

Haemophilus influenzae began developing resistance, principally with the production of beta-lactamase during the early 1980s, and at this point we're up to, in various parts of the country, between 30 and 50 percent of Haemophilus resistant to beta-lactams because of productions of beta-lactamase.

There also is a alter-penicillin binding protein characteristic of some Haemophilus that exhibit their beta-lactam resistance on this basis, which is the exclusive way that pneumococci exhibit beta-lactam resistance. And of course, this has been a relatively recent phenomenon that I'll show more

detail on in just a minute.

So that on the average across the United States today, with great exceptions in certain cities, about 25 percent of pneumococci have reduced susceptibility to beta-lactam drugs. In some cities that rate is as high as 60/70 percent, and in others in the low teens.

Now, I think it's interesting to look at bit -- and we're going to focus now pretty much exclusively on pneumococcal resistance because that is the emerging problem at this time and at the end of the 20th century.

I'm going to illustrate some data from the St. Paul-Minneapolis Twin Cities Area of Minnesota because Minnesota has had a surveillance project on-line since April 1995, and is one of a half-dozen pneumococcal surveillance states in the United States. And I'm just familiar with these data the most, and believe they fairly adequately represent these other surveillance sites.

And the two bars here simply illustrate the prevalence of invasive pneumococcal disease during the last two-thirds of 1995 and the first three-fourths of 1996. You'll notice that invasive pneumococcal disease is most common here at the infant and early

childhood ages, and then increases with later years -- not much difference between the two years.

And when we look at oxacillin resistance, which is a reasonably good, not perfect reflection of penicillin resistance among pneumococci, you'll notice that at all of these age groups, oxacillin resistance is demonstrated with a slightly higher rate in the infant, early childhood group and in this older group out here, but statistically no difference in the prevalence of resistance across the age spectrum.

When we speak of penicillin-resistant pneumococci, again from these data in Minnesota with about 80 percent sensitive, 10 percent showing intermediate resistance, these have MICs between .01 and .1, and resistance organisms -- you'll see that many of the other anti-microbials show greater activity against resistant pneumococci, specifically amoxicillin, showing greater activity against these same strains of pneumococci, cefpodoxime, several of the cephalosporins.

Clindamycin is probably the most active, oral anti-microbial agent against the more resistant pneumococci, and we're particularly mindful of trimethoprim sulfamethoxazole which does not do very well against the resistant pneumococci, for among

parenteral drugs, vancomycin is the only parenteral drugs that has not shown in this country, resistance to the penicillin-resistant pneumococci. There have been vancomycin-resistant pneumococci reported elsewhere in the world.

When we look at the concordance of penicillin resistance with resistance against other drugs -- amoxicillin, cefataxime, clindamycin, erythromycin, trimethoprim sulfa, and vanco -- and drop down to this line here, among the 15 highly-resistant, penicillin-resistant pneumococci from the Minnesota study, you'll notice that 7 of these 15 had either immediate amoxicillin resistant, eight were highly resistant -- demonstrating the increased activity of amox over penicillin; cefataxime, only two of the 15 organisms were highly resistant to cefataxime; only one highly resistant to clinda; trimethoprim sulfa didn't do very well; clinda and vancomycin did quite well against these resistant organisms.

So with that information in mind, many have asked the question, given the emergence of these resistant organisms, should we be treating acute otitis media at all? And I would argue that the answer to that question is yes. It's an infectious

disease caused by bacteria as we've just illustrated.

I'm going to show you in beta in just a minute that there has been a striking decrease in rates of acute mastoiditis with antibiotic treatment. And I'll show you in just a moment that there is a better treatment outcome when antibiotics are used to treat acute otitis media.

The single, largest, clinical trial looking at no treatment of acute otitis media is barely applicable to clinical practice in the United States. There were tremendous difficulties with the design of that study: using general practitioners who were not validated for the uniformity of their diagnostic skills in detecting this disease; and none of these children were younger than two years of age, while at least half of the children getting treatment for AOM in the United States fall into this younger age group.

So I have a lot of trouble extrapolating the Dutch, no treatment study to our use of antibiotics for treating AOM in the United States.

Now, I know you can't see all these numbers, but this is a review, probably the best I've seen published by Steve Berman in Pediatrics two years ago in 1995. And Dr. Berman summarized the literature of no antibiotics treatment and sulfonamide treatment for

acute otitis media looking at complicating rates of acute mastoiditis.

And down this column -- and there are several hundred cases, well over a couple thousand cases here -- summarized and many with, probably most with different designs, between 1939 and '54. You'll notice that between nine percent which is the low, and 40 percent, 70 percent of these cases were complicated by acute mastoiditis.

In the parallel studies where sulfonamide was used as a comparative, you'll notice dramatically lower -- none of these rates exceed 20 percent and most of them are in single digits. So here with a very narrow spectrum drawn, particularly for those three major pathogens, we see a tremendous reduction in mastoiditis with antibiotic treatment of AOM.

This to me, is one of the more powerful reasons that I believe we need to continue to treat, bona fide, acute otitis media with antimicrobial drugs.

Now, without a doubt, there is spontaneous resolution of acute otitis media. And this is still my favorite study demonstrating the spontaneous resolution of otitis -- a very carefully controlled study by the Pittsburgh Group, published in Pediatrics

in 1991; Phil Kaleida was the first author of this study -- for several hundred children with AOM that was either mild or categorized as moderate-severe, were enrolled in this trial.

And those with mild disease were treated with placebo and those with severe disease were treated by myringotomy -- which we know has a very transient effect on the healing process of acute otitis media and is a reasonable placebo treatment, particularly for young children with severe disease at that stage.

And you'll notice that this placebo treatment cured 92 percent of those with mild disease and 76 percent of those with severe disease, strongly suggesting that many children with AOM don't need antibiotic treatment; that they will respond spontaneously and heal their middle ear condition.

The problem is, we can't predict who these children are, prospectively, and so we end up treating all of them. And you can see that for both mild and for moderate-severe disease, there is a significant treatment effect when amoxicillin was used, and the treatment effect is greater, as you might suspect, for moderate-severe disease and not so great -- only a four percent rate difference -- for those with mild

disease. So there is a treatment effect in even mild acute otitis media.

I submit that we pick antibiotics for acute otitis media -- which is a bacterial infection of the middle ear -- using exactly the same principles that we use for picking an antibiotic in any other infectious disease.

We identify ideally, the causative bacteria, either by culturing the middle ear or by knowing community patterns and epidemiology of the disease. We pick antibiotics based on the susceptibilities of the causative bacteria. We know the pharmacokinetics of those drugs and their efficacy in the middle ear, and then we measure treatment outcome.

And what I'd like to do is, in the remaining time, walk through some of the data in this regard that give us some guidance in selecting these antibiotics.

Understanding the in vitro and in vivo activity of an antimicrobial drug is of course, absolutely essential in selecting an antibiotic. The in vitro measure is determining the concentration of an antibiotic that -- the minimum concentration that either inhibits or kills the organism called the minimum inhibitory concentration or the minimum

bactericidal concentration.

But really, the rubber hits the road in this case, in the middle ear -- in the case of meningitis, in the brain -- by understanding the relationship between this in vitro measure of bacterial susceptibility and the concentration of the antibiotic over time at the site of infection. And so this in vivo relationship is really what we're trying to predict through both the in vitro assessment of susceptibility and the pharmacokinetic data.

Now, it's important to see what's happened to the MICs of these pneumococci over time. And these are data, some of which that I'm going to show you in the next few slides, have not been published and were presented as part of a CDC symposium this past spring in increasing pneumococcal resistance.

If we look at MIC_{90}, these are the MICs at which 90 percent of pneumococci in this case, are inhibited, you'll notice that for all of these antimicrobial drugs, there has been a very steady increase in MIC_{90} over time, with amoxicillin from .03 to 1, with cefaclor from .4 to 128.

Cefixime of course, never did very well; cefuroxime has stayed rather stable; the macrolides are showing increasing resistance -- pneumococci are

showing increasing resistance to the macrolides now with MIC_{90}s that far exceed easily achievable concentrations in fluid compartments -- and particularly in the middle ear -- including azithromycin. I'll show you some in vivo data in just a few minutes on this.

Now, pneumococci fortunately for all of us, don't do very well when they alter their penicillin binding proteins enough to get up to MICs of 8 micrograms/ml. And I've heard Alex Tomasz, who is one of the experts in this area of pneumococcal resistance say that it's unlikely that we're going to see pneumococci survive in the world with MICs much over 8 micrograms/ml.

So you'll see that we certainly have increasing problems with these very resistant pneumococci, but there may be a threshold here at which we're not going to see organisms with much greater penicillin MICs than eight.

How do we measure antibiotic effectiveness? Well, ideally as I mentioned earlier, we measure the bacteriologic efficacy. This is done easily if you have a compartment like the urinary bladder where you can simply get another urine sample on antibiotics and see if the urine has been sterilized by the drug that

was picked.

A little harder with the middle ear but we'll look at data here that I'll present, and I'm sure data by the sponsor later on, on the bacteriologic efficacy of antimicrobials for acute otitis media.

Clinical efficacy is the surrogate that's often used to measure antibiotic effectiveness, and I'll show you some of the problems with that in just a moment. Pharmacokinetic surrogates get us a bit further away but are important in understanding relationships of antibiotic concentration in time in the middle ear. And Dr. Craig has done some eloquent studies in this area that I will capture in a couple of slides in just a few minutes.

And of course, the bottom line here is, does the infection that you were trying to treat, relapse with the identical organism, and now that we have pulse field electrophoresis it's actually possible to find out if the same strain that caused an initial infection is causing the relapse.

So these are the methods that we have to measure antimicrobial effectiveness in acute otitis media. Let's just take a look for a minute at some of these pharmacokinetic surrogates of antibiotic

efficacy.

And I illustrate here MIC_{90}s of penicillin-susceptible, intermediate and resistant organisms. And if we just look at the first line here with penicillin, the penicillin susceptible pneumococci are defined as having MICs less than .1, intermediate .1 to 1, and penicillin-resistant pneumococci having MICs over one.

The average peak serum level after a usual, oral dose of penicillin, is on the order of one to two micrograms per ml, which barely takes us over the intermediate range of these pneumococci, and ideally we'd like peak serum levels that are four to eight times the MIC, illustrating here that penicillin for all but the susceptible organisms is not a very good pick when it's being given orally and achieving these serum concentrations.

Amoxicillin does a bit better with average peak serum levels of three-and-a-half to seven, exceeding in some cases the penicillin-resistant organisms -- excuse me, the amoxicillin-resistant organisms, with MICs exceeding 2 micrograms/ml. And you can go down the line here and see the particular concerns -- for example, with cefixime, peak serum concentrations of three to four, barely exceeding the

cefixime susceptible organism down here, and the like.

Dr. Craig published this study last year in Pediatric Infectious Disease Journal illustrating the relationship between the time that a drug exists in the middle ear space -- in the serum -- over MIC of the organism, and the response of the middle ear to bacterial infection.

Looking at both pneumococci and Haemophilus, beta-lactams, macrolides, and trimethoprim sulfa from a number of different studies, and just tried to fit a line illustrating this relationship between percent time over MIC in the plasma compartment with bacteriologic cure.

And you'll notice that when the percent time drops much below 40 to 50 percent, the bacteriologic cure rate drops rather dramatically. And it's been these data that have suggested that if we have a pharmacokinetic surrogate with time over MIC that exceeds 40 to 45, 50 percent, we probably have a pretty good measure of antimicrobial efficacy.

Let's take a look at some of the bacteriologic endpoints then, of antibiotic efficacy getting a little closer to a true measure of antibacterial action. My attention was first focused on bacteriologic efficacy when we were looking at

cefixime data, and I summarized data that had been published by Howie Johnson and Owen, all comparative trials of cefixime and amoxicillin.

And I was struck that accumulating these data with 158 cefixime cases, 174 amoxicillin cases, that actually cefixime for all pathogens, seem to do better than amoxicillin, in fact, significantly better. And yet when the specific bacterial activity was looked at for the pneumococcus Haemophilus and Moraxella, we see that cefixime cephalosporin had considerable gram-negative activity exceeding that of amoxicillin, but very poor pneumococcal activity.

And so it's only when you've drilled out into the trees a little bit below the clinical response rate and the aggregation of all organisms, that you actually see the antibacterial inferiority of this particular drug reflected by looking at these specific, bacterial response rates.

Now, a number of investigators -- I shouldn't say a number because there are relatively few that have had the luxury of being able to look at on-treatment cultures, a methodology that I am highly supportive of because I think it's the only way to tell us whether an antibacterial drug is actually working in the middle ear space, giving histologic

variation in the condition I showed earlier -- have tapped these ears on treatment.

Leibovitz is with Ron Dagan in Israel and some of the more recent studies have come out of his unit in Israel, and here I'm summarizing data that were presented at the ICAAC a year ago comparing cefaclor with cefuroxime, cultures performed on day-5 on treatment in cases of pneumococcal AOM. Here are the groups of penicillin susceptible, intermediate and resistant pneumococci.

And you'll notice that as the MIC increased so did, for both of these drugs, are the bacteriologic failure rates. So 58 percent of the 26 isolates that had MICs over .5 failed cefaclor treatment; three of the five treated with cefuroxime axetil failed treatment. A very clear relationship between increasing MIC and bacteriologic response rate, which is exactly what you'd predict from the pharmacologic surrogates that we were looking at earlier.

A study by Hoberman that was just published in the Peds ID Journal, looking at the few cases here -- I'm sorry, not few; there were a number of cases here that were cultured with penicillin MICs of susceptible intermediate resistant, again showing an increased rate of bacteriologic failure -- sorry, I'm

getting ahead of myself -- of clinical failure in the more resistant isolates.

This is a summary that Dr. Dagan gave the group at the CDC in March, looking at an aggregation of all of his 2-tap studies with amoxicillin, cefuroxime, cefaclor, azithromycin, ceftriaxone.

Again showing -- and if we just focus on the susceptible, intermediate and resistant pneumococci increased rates of bacteriologic failure for the resistant organisms compared to the susceptible organisms. So MIC is a very important parameter in measuring antimicrobial efficacy.

Virgil Howie, who is the single individual that I create with advancing the treatment of acute otitis media in the United States beyond the black box era of picking the drug without understanding the nature of the infection, and particularly the susceptibility, to the present era where we're treating the disease based on true infectious disease principles, summarized a vast amount of information in a table published in clinical infectious disease in 1992 that I have summarized in this graph; that compares bacteriologic outcomes -- these are all 2-tap studies and an aggregation of a number of studies -- comparing placebo treatment with a number of different

antimicrobials.

And here it's important to note that pneumococcal disease -- these purple bars -- treated with placebo, only spontaneously resolves in the studies that looked at this about 20 percent of the time; 80 percent of this disease persists.

On the other hand, Haemophilus influenzae has about a 50 percent spontaneous resolution rate, and some have suggested with very small numbers -- which is why it's not included here -- spontaneous resolution rates with Moraxella catarrhalis that are on the order of 60 to 70 percent. But I think the numbers are too small to say much about that.

As you go down the line -- and remember that these studies were done prior to the emergence of all the penicillin resistant pneumococci we have today -- you'll notice that amoxicillin, and of course amox/clavulanate, have tremendous activity against these pneumococci with persistent cultures that drop from 80 percent down to about five percent; cefuroxime, 100 percent active; cefixime not so good; cefaclor not much different than placebo.

Haemophilus influenzae, again here, because of beta-lactamase production, amoxicillin didn't do so well. I'm not sure exactly why in these studies the

addition of clavulanate didn't offer much additional activity, although we know from comparative trials this is quite a bit better.

And the second generation and third generation cephalosporins, except for cefprozil and cefaclor compared to placebo, are doing quite a bit better. The increasing evidence, both with clarithromycin and azithromycin from Dagan's group showing not very good activity of these antimicrobials against Haemophilus influenzae in 2-tap studies.

Doesn't make any difference whether you eradicate an organism early or not -- and this has been an oft-discussed subject. Do these 2-tap studies that are performed at three, or four, or five, or six days, really make a difference in treatment outcome of the patient.

Here again, Dagan's group has been tremendously helpful at adding information data to that question. He summarized several clinical trials -- again at this March meeting and was presented in abstract a year ago at the ICAAC -- looking at the treatment outcome of children whose ears were either culture-negative -- there are 39 of those -- or culture-positive on day-4 or -5, and then looking at their clinical status on day-17 after the conclusion

of treatment.

And you'll notice that those with negative culture only had a clinical failure rate on day-17 of three percent, whereas those with a positive culture on treatment had a 10-fold higher -- greater rate of clinical failure. So it does make a difference whether you sterilize the ear early or not.

Clinical outcomes, unfortunately as I've alluded to, don't accurately predict bacteriologic curer. Carlin and the investigators in Cleveland summarized their data from a number of clinical trials in Journal of Pediatrics in 1991, looking at 293 children who had culture-confirmed, bacterial acute otitis media, and found that the sensitivity of the clinical outcome -- so clinical success with bacteriologic success occurred 93 percent of the time.

So the clinical assessment of success was quite sensitive for bacteriologic eradication. But the specificity of the clinical assessment was about as good as guessing. It was very poor. The clinical assessment of failure -- 15 cases in the case of bacteriologic failure, only predicted 37 percent of the bacteriologic failures.

So clinical assessment, because of its low specificity -- not because of problems with

sensitivity -- is a problem in measuring middle ear outcome of antimicrobial treatment.

We and the group in Dallas have asked the question, is it possible, given the greater activity of amoxicillin for this penicillin-resistant pneumococci -- to treat penicillin-resistant pneumococcal otitis using higher doses of amoxicillin? And here we're focusing only on pneumococcal, not on Haemophilus or Moraxella disease.

From a study that was presented by Hoberman at ICAAC in 1995 and subsequently been published, and Mike Jacobs who I've seen here is intimately involved with, looked at the susceptibility distribution of 267 pneumococcal isolates at 30 centers across Europe and the United States during a fairly recent period, found that 90 percent of these isolates had amoxicillin susceptible MIC at or below .5; about eight-and-a-half percent were intermediate; and only one-and-a-half percent were resistant.

So we wondered if it might be possible to exceed that level of 2 micrograms/ml for a sufficient period of time -- ideally 40 to 50 percent of time -- in the middle ear using larger doses of amoxicillin. And we have in press in Pediatric Disease Journal and have presented previously, a study that we did in

collaboration with Tasmee Chonmaitree at the University of Texas, Galveston, where we gave 26 children with acute otitis media a single dose of amoxicillin on treatment at major intervals after their middle ears were tapped, as part of the 2-tap study.

These intervals were selected to be able to plot using pharmacokinetic software -- and I've done that without the pharmacokinetic plot here -- but simply to illustrate the middle ear concentrations of amoxicillin in these children that got a single dose of 25 mg/kilo.

You'll notice that there's quite a range in amoxicillin concentrations among these children -- and this is not on a log plot; this is a linear plot -- and I've just drawn across here that MIC of 2 micrograms/ml representing the threshold between intermediate and resistant pneumococci.

And you'll notice that the curve clearly gives us concentrations that are up in the 40 percent over this MIC range, and the majority of these dots exceed that 2 microgram concentrations. So a 25 mg/kilo dose of amoxicillin might very well handle a lot of these infections caused by even amox intermediate pneumococci.

Dr. McCracken's group in Dallas did us one better and increased the dose in 17 patient to 45 milligrams per kilo. This has subsequently been published this year as a letter in Pediatric Infectious Disease Journal showing that at this dose -- again, I've drawn this 2 microgram threshold here -- that virtually all of the middle ear fluid concentrations measure between one and three hours -- exceeded that threshold.

So it may be very possible, given the inability of pneumococci to probably exceed an 8 microgram/ml MIC, to achieve concentrations that are active in the middle ear using a very inexpensive, readily available drug.

How do we put all this together for the clinician in selecting drugs for treating acute otitis media? And I'm not going to get into this very much but I just want to drill down here to the bottom line. In clinical use of antimicrobials, we teach clinicians to assess the child for risk of treatment failure.

If it's a child that's had multiple episodes of acute otitis media, that had those episodes early in life but has recently been exposed to antibiotics, that's in a daycare center, they deserve an initial treatment with a much broader spectrum drug than the

older child who's having a first or second episode, that's not in daycare, that has few risk factors, where a drug like amoxicillin might be perfect.

We suggest that they select an initial antibiotic and as they're there, particularly with a high risk child, they plan right then what they're going to do when the child fails treatment. We are advocating amoxicillin for that low risk child as the initial drug, mainly based on mild otitis, high spontaneous resolution rates, low cost, but not necessarily very good pneumococcal coverage.

Trimethoprim sulfa as a several steps down, second-best alternative to amoxicillin, but clearly the preferred drug for me is amoxicillin at higher doses of the drug, none of which have been studied beyond the pharmacokinetic studies I show you, and all of which need desperately to be studied.

For the high risk child, initially or subsequently, either amoxicillin/clavulanate or ceftriaxone -- which you're going to discuss further this morning -- probably cefuroxime axetil, and in some parts of the country, cefpodoxime or cefprozil where pneumococcal resistance hasn't become a big problem -- a reasonable broader spectrum drugs for the high risk child.

Let me end up with illustrating just a couple of studies that have looked at shorter course -- you're going to be looking at the shortest course with single dose ceftriaxone -- but shorter dose oral treatment and in fact, longer course treatment of acute otitis media, and then I'll stop.

This is a study that looked at cefuroxime axetil, a multi-center study that this panel may actually have, I suspect, reviewed at some point in the past, looking at 5- versus 10-day treatment compared to amoxicillin/clavulanate at ten days.

And if we drop down here to clinical failure rates, there was no significant difference among the 5/10-day cefuroxime treatment groups, compared to the augmentin 10-day groups, no difference in cure or clinically improved rates, nor any difference in recurrence rates.

Again, those were the clinical data that were not bacteriologically specific. Some of these children -- not many -- had middle ear taps to look at specific antibacterial activity with reasonably good assurance marching across from five to ten days of cefuroxime to ten days of amox/clavulanate; that these regimens were equally effective on a bacteriologic perspective for the pneumococcus and for Haemophilus

influenzae.

A cautionary note, however, was raised with the recent publication by Hoberman in Peds Infectious Disease Journal this year, looking at the age-specific activity of these shorter course treatments. In this particular study the investigators compared three doses a day, ten days of amox and clavulanate to a b.i.d. regimen that had a higher dose of amoxycillin, lower dose of clavulanate for ten days, and that same preparation for five days. Here are the doses of amox and clavulanate per kilo.

Clinical success rates at day-12/14 at the end of treatment that looked good, but when the investigators drilled down to age-specific outcomes, they found that the 10-day b.i.d. regimen had significantly better outcomes than the 5-day regimen for those children that were younger than two years of age, and borderline better outcomes for the children who were two to five years of age.

Suggesting that we should probably be careful with respect to age in looking at shorter course treatments. And I think that is my takeaway message from short course treatment of acute otitis media; that age may be a very important covariate in determining antibacterial activity.

And finally, a study by Ellen Mandel -- again from the Pittsburgh Group -- asking the question, is longer treatment beneficial, more beneficial than standard 10-day treatment for acute otitis media? And again, in a very well-designed study where amoxicillin was given to three groups of patients for the first ten days and then for the next ten days the first group received an additional course of amoxicillin. This group went on to amoxicillin/clavulanate and this group to placebo, all in a double-blind design with about 90 patients in each group.

You'll notice as you'd hope, the effusion-free states in all three groups were the same at the end of ten days of treatment with the same drug. But there was significant improvement in both the amoxicillin and the amox/clavulanate groups with respect to placebo over the 20-day outcome in this study. Suggesting that perhaps in some children, longer course treatment may in fact, be beneficial.

I'm going to stop at that point and Bill, if there are questions I'd be glad to answer them, or move along, whichever.

CHAIRMAN CRAIG: Yes, I think we're going to need to move on, and we'll definitely -- you're going

to be around for a while and we'll get to the questions later on.

So I think we need to move on to the sponsor's presentation, and they will have the full time that's allotted, which I think was an hour and fifteen minutes.

MS. da SILVA: Thank you. Good morning. I'm Loni da Silva, program director for Regulatory Affairs at Hoffmann-La Roche. This morning we will be discussing Rocephin™ as a single, IM injection for the treatment of acute otitis media.

In this morning's presentation we will be describing to you our clinical development program which consists of several studies: a pharmacokinetic study conducted in Iceland, two bacteriologic studies conducted in the U.S., as well as five clinical studies -- four of which were conducted in the U.S. and one in France.

You'll hear in our presentation this morning that a single dose of ceftriaxone for the treatment of acute otitis media offers the following benefits: a favorable, pharmacokinetic, pharmacodynamic, and pharmaceutic profile; also has bactericidal activity, in vitro, as well as in vivo activity against the three basic causes of pathogens.

The possibility of increasing resistance is minimized due to PK properties and sustained duration of bactericidal activity in the middle ear fluids.

The other efficacy which we will show you is comparable to that of standard treatment as well as a well-established safety profile. You also hear of the advantages of a single dose parenteral therapy, and with a single dose there is guaranteed, 100 percent, full course treatment and compliance.

Parenteral preference has also been shown for a single IM dose, therefore, a single dose of IM Rocephin™ in the treatment of acute otitis media offers a significant addition to the armamentarium for the treatment of acute otitis media.

Our presentation this morning will consist of three speakers. First we'll have Dr. Jerome Klein from Boston University School of Medicine, Boston, Massachusetts. His presentation I think, will complement Dr. Giebink very nicely with an overview of otitis media and its treatments.

We'll then have Dr. Jeffrey Blumer from Rainbow Babies and Children's Hospital from Cleveland, Ohio, who will be discussing the pharmacokinetic and pharmacokinetic properties of ceftriaxone in acute otitis media.

And lastly, Dr. Jonathan Solsky from Hoffmann-La Roche will be presenting our efficacy and safety data of ceftriaxone in acute otitis media.

Dr. Klein, would you please come to the podium?

DR. KLEIN: Good morning, colleagues. My role this morning is to discuss selective aspects of acute otitis media and the role of the drug we'll be discussing, single dose ceftriaxone. Dr. Giebink's discussion was so comprehensive that you will be hearing throughout the morning, corroboration of some of the data that he has presented. Fortunately, I chose different slides so that they won't --

(Laughter.)

Dr. Giebink and I were on a program on one occasion where he was the third speaker who showed the same slide. And he pointed out that in Minnesota that's an important point in continuing medical education -- to show the same slide three times.

(Laughter.)

The diagnosis of acute otitis media is increasing significantly over the past couple of decades. These are CDC data that show for office visits, the numbers have increased from about ten million for this diagnosis in 1975, to more than 25

million in 1990, and there are data that suggest that that number is in excess of 30 million in the mid-1990s.

This is a disease of infants. The highest age-specific attack rate is six to 18 months, and so the largest increment has come in the group of children less than two years, although the increased number of office visits has been in the toddler age and the school age children as well.

But the disease for the most part is a concern to children and to parents in the first three years of life. If you've managed to escape otitis media during the first three years you won't have problems thereafter, except for perhaps episodic occurrences.

The reasons for the increment remain largely unknown, but two features appear to be associated; that is, the increased number of young children in daycare, the large number of infections -- respiratory infections that they encounter -- and because they are otitis-prone during the first three years of life, they get a cold plus otitis media.

It may be that access to care with increased numbers of patients in managed care programs is also a reason for this increment. Whatever it is, it is a

large problem and the single most frequent cause for visits to pediatricians.

Dr. Giebink presented the pathogenesis in a wide sequence, and I'll just reiterate that with this diagram indicating that there probably is an antecedent, viral, or allergic event that leads to congestion of the mucosa of the upper respiratory system, and the mucosal blanket encompasses the eustachian tube as well as the middle ear.

If that congestion is sufficient so that one has obstruction at the narrowest portion of the eustachian tube, the isthmus, then the secretions that are constantly being formed in the middle ear have no egress, they pile up behind, fill the middle ear space so that one now has a fluid-filled space, and bacterial pathogens that are constantly in flux and move out when the eustachian tube is open, are now trapped behind that obstruction, they multiply, and an abscess ensues.

The role of the antimicrobial agent is to sterilize that abscess and to produce clinical resolution and to reduce the proportion of complications that may occur from this abscess in this particularly important area in the skull.

In 1992 the IDSA-FDA guidelines were

presented and formed the basis for many clinical studies of acute otitis media that have been presented to the Food and Drug Administration. Essentially there are two components.

One is the identification of the presence of fluid in the middle ear. If one has an air-filled middle ear space, that's not acute otitis media -- at least not at that time. So it's important to identify middle ear effusion.

We believe that pneumatic otoscopy is an important component in identifying limited mobility of the tympanic membrane or evidence that there is fluid present as can be visualized by an air fluid level or bubbles.

For our study we included more rigorous criteria involving the instrumentation of tympanometry and acoustic reflectometry, but these need not be incorporated into all trials. However, I think it does lend an element where there are multiple observers of objective assessment.

The middle ear effusion should be accompanied by an acute sign of illness that may be specific as an ear sign, or may be non-specific. The children may have ear pain, otalgia, or drainage, otorrhea, or a perception by the parent of some

diminished hearing or even vertigo.

Non-specific signs -- and the asterisks indicate the more important ones -- are: fever* -- new onset; irritability*; lethargy; change in feeding habits manifested by anorexia*, or vomiting*, or diarrhea. Some of them are relatively non-specific.

But it's clear that visualization of the tympanic membrane -- that is, just looking at a tympanic membrane -- is inadequate; that one needs to have the identification of the diminished mobility and in fact, in the needle aspirate studies, to identify the bacteriology of the contents of that fluid -- that the color of the membrane was often not a significant factor in determining whether it was bacterial or non-bacterial.

The expectation is that children with the appropriate antimicrobial agent, will resolve substantially in 48 to 72 hours, and that by 10 to 14 days after a 10-day course, or even a shorter course, that those children will have significantly resolved their clinical signs.

It's a subtlety as to whether there is pure -- meaning all the signs have been completely eliminated -- or whether they have been significantly resolved, that would be identified by improvement.

And in our study and those of others, pure /improvement at 14 days has been given as a sign of drug efficacy.

It has been well documented that superficial cultures -- nasopharyngeal cultures -- are inadequate to identify the organism that is present in the middle ear space. It is frequently sensitive -- that is, the organism is present in the nasopharynx -- but it may not be specific; there may be other pathogens present as well.

So to identify the microbiology of acute otitis media it is necessary to do a needle aspirate. And subsequently, I will be showing data that Dr. Giebink's already presented, about double aspirate studies. An initial tympanocentesis to identify the bacterial pathogen, and then at some time after the onset of therapy, another tympanocentesis to identify whether or not that fluid had been sterilized.

These data are gathered from a large number of studies performed during this period of time. The figures are reasonably consistent throughout the studies, although there is a range that goes from 27-52 percent for the pneumococcus, from 16-52 percent for Haemophilus influenzae, but these are the two major players. M. catarrhalis is less, and there are

some Group A streptococci, staph aureus and other bacteria.

In most of the studies by usual bacteriologic techniques, about a quarter of the specimens do not have a bacterial pathogen present. Now, PCR is undoubtedly going to decrease this number. Exactly what PCR-positive, culture-negative means, I think we'll have to decide in the future.

But one may use enrichment techniques, direct plating, that would be more precise in identifying how many of these are non-bacterial. Suffice to say though, we're dealing with pneumococcal and Haemophilus -- non-Type O Haemophilus infections.

In the pre-antibiotic era many children did resolve, some accompanied by that abscess, putting pressure on the tympanic membrane, central ischemia occurring, and then the membrane rupturing. With the abscess contents being discharged the child had resolution of the signs and symptoms. And many children either had that or had myringotomy to create that incision and drainage.

The membrane is very vascular and so it may seal quickly as well, and one would have a renewal of the signs and symptoms of disease. But all children didn't go on to dire consequences who had acute otitis

media. But it was a frequent reason for hospitalization. A quarter of the admissions to Bellevue Hospital for pediatrics in 1932 included complications of acute otitis media, be they mastoiditis or other intracranial complications.

Today, we don't see this pattern in the United States. Mastoiditis in the general pediatric or children's hospitals, is uncommon. We see about one case ever couple of years.

However, in some areas, they may be seeing more, and those areas were developing countries where patients do not have access to medical care and essentially they are living in a pre-antibiotic era or there are selected areas in Europe where they have chosen not to use antimicrobial agents. And they are accepting a certain number of cases of mastoiditis.

The withholding of antibiotics is a practice in Holland, and as you read the studies that Dr. Giebink mentioned by Van Buchem and colleagues, there are a couple of cases of mastoiditis that do occur.

In this paper from Germany by Hoppe in 1994, he related the number of cases of mastoiditis that were occurring in Tubigen, and the increased numbers as the practice of withholding antimicrobial agents became more prevalent in that community.

So there is a trade-off if one chooses to observe rather than treat initially, the diagnosis of acute otitis media. And I concur with Dr. Giebink's conclusion that acute otitis media is a treatable disease.

There are 13 drugs that are approved for the indication of acute otitis media, and I presented them in the order of the number of doses per day, ranging from erythromycin-sulfisoxazole or pediazole which is administered four times a day, to the newer preparations -- cefixime, ceftibuten -- one time per day for ten days, or azithromycin, one per day for five days.

From the data that are presented to the Food and Drug Administration, they are safe and effective and clinically there is no dominant drug; that is, they are all within the statistical likelihood of the equivalence.

However, there are microbiologic differences. Dr. Giebink presented these data in a different -- in a bar graph -- but I think they are compelling and important to the story that we'll be discussing today.

These are double aspirate studies. The initial aspirate is done before therapy, and that

identifies the organism. In this column, these children had a pneumococcus isolated. These children had Haemophilus influenzae, non-typable strains isolated, and they form the denominator.

Then either placebo or drug is administered and two to seven days later another aspirate is performed to identify either persistence or sterilization of that middle ear fluid. And here, the numerator is persistence.

The placebo data identify that even in bacterial otitis media there is spontaneous resolution. Modest in the pneumococcal otitides -- 19 percent -- so 46 of 57 ears with a pneumococcus isolated initially, 46 persisted. But interestingly enough, in Haemophilus influenzae almost half were gone. Only 13 of 25 persisted.

I think this is corroborated in a way by the amoxicillin data. As amoxicillin quite effective, only eight of 136 strains persisted. In this case, if there was non-beta-lactamase-producing strain of Haemophilus influenzae, only three of 23. But if it was a beta-lactamase-producing strain, keeping the beta-lactam ring of the susceptible penicillin, you virtually have placebo.

So there was persistence in the majority,

very much as had been identified in the placebo, corroborating, I think, that point that amoxicillin is not going to work in those strains that are beta-lactamase-producing, but those strains also have a very high rate of spontaneous resolution.

Cefaclor -- and Dr. Giebink identified the data from Dr. Dagan as well -- the relatively modest benefit. Cefixime, similarly, about 25 percent of failures; better against Haemophilus influenzae. Clarithromycin, excellent against pneumococci, not against Haemophilus influenzae -- at least in terms of this microbiologic endpoint.

Trimethoprim sulfa, reasonably good, but I would be concerned today because of the high rate of pneumococcal resistance in most communities throughout the United States, so I probably would not have put it in that first box of first-line drugs.

Ceftriaxone, because of the high concentrations achieved, this is single dose initially, then the aspirate is performed three days later, uniform sterilization of the pneumococci and Haemophilus influenzae.

These data were gathered in the '80s before there was a significant proportion of intermediate or resistant strains, and so we must assume that all of

these strains were susceptible penicillins. Nevertheless, this parenteral agent -- the only parenteral -- given as a single dose, uniformly sterilized the middle ear fluids.

In looking at more recent data -- and Dr. Giebink has presented some data from the group in Israel, and they're about the only ones who are producing this valuable information -- here's even a more up-to-date slide, Scott.

And this is Dagan's data from ICAAC 1997, and they don't address the ceftriaxone issue but they don't address the penicillin-sensitive or resistant issue when evaluated against amoxicillin, cefaclor, and azithromycin for penicillin sensitive strains identified as less then .1. So the resistance includes the intermediate resistant category.

Nevertheless, there is a trend in this dual-aspirate study to more failures in the penicillin-resistant category, and this is amplified in the cefaclor group where more than half failed to sterilize the middle ear fluid at three days.

For azithromycin the standard was azithromycin-sensitive or resistant, and as you can see, azithromycin is excellent for the sensitive strains but not for the resistant strains.

In looking at those children who had Haemophilus influenzae, amoxicillin failed in nine of 33; six of the nine were beta-lactamase-producing strains, and so failure would have been expected; cefaclor about 50 percent; azithromycin actually, a majority of the strains persisted at the 3-day period.

So the technique of dual-aspirate is a very valuable one in providing us information about the ability of a drug to achieve concentrations at the site of infection and sterilize that middle ear fluid.

Marchese has presented data very similar to the information that Dr. Giebink presented; that if you achieve sterilization of the fluid, that you will have clinical success in the '90s. There probably are a few where there's a concurrent viral infection where you may not have a clinical resolution because of the other element.

If you have failure, you still may get 60 percent resolution because of other elements of the resolution that may occur. So that these data are important I think, in comparing drugs and assessing their efficacy. We need more data obviously, with the newer and more resistant strains.

There is no perfect antimicrobial agent for acute otitis media. I think the list that Scott gave

based on the CDC working group in the spring is a very reasonable one about dealing with initial therapy and then failures. And most pediatricians would concur that in the simple, uncomplicated, initial case, amoxicillin remains the drug of choice. But we do need backups.

But there are limitations in the antimicrobial spectrum. Amoxicillin as noted, is beta-lactamase susceptible, so for those Haemophilus or Moraxella, then the small number of them that will not resolve spontaneously and require an effective drug, amoxicillin will fail.

Trimethoprim sulfa, as is true for all the sulfonamides, would be ineffective for a Group A streptococcal otitis media. Cefixime and ceftibuten would not be effective for intermediate or resistant pneumococci, and you've seen the data about macrolides and their failure to sterilize middle ear fluids which Haemophilus influenzae is the pathogen.

Diarrhea is a concern with amoxicillin/clavulanate, though the new formulation appears to have decreased the proportion of children who have diarrhea. I have had a couple of patients who have had Stevens-Johnson Syndrome, and these are hand-wringers when you happen to have a patient for

whom you have no therapy.

There's no way except waiting out this mucosal and skin disease. And cefaclor had this interesting serum sickness-like reaction that appears to be unique to this agent.

It's clear that for working families, oral dosages need to be no more than two a day; that administering drug in the daycare center or school becomes problematic. And so the three or four times a day preparations are less favored.

Some of the better drugs -- cefpodoxime, cefuroxime axetil, and even clarithromycin -- have problems of palatability. So why add a 14th agent? First, it will be the first parenteral agent -- it is the only parental agent.

Second, it does have the capability against the three major pathogens. It can achieve, as will be -- the documentation will be given to you by Dr. Blumer -- that the high concentrations should encompass the currently identified penicillin resistant pneumococci. Being beta-lactamase stable, it also is effective against the Moraxella and Haemophilus influenzae.

So the high concentrations of drug in the middle ear, uniformly eradicates the common bacterial

pathogens as was identified in the Howie data from the '80s, and we speculate that it will include the resistant strains also, because the concentrations should be above current MICs for resistant strains.

In my usage, off-label now, the compliance issue is a major reason for considering the drug. There are some children who struggle with oral medications, who have difficulty with two to four times a day, 10-day oral regimens.

There's some parents who become frustrated, angry, feel guilty if they don't comply with the 10-day oral regimen. There are some children who are vomiting or who are ill and won't tolerate an oral medication. So a single dose parenteral is a child issue and a parent issue in terms of satisfaction of our consumers.

The safety profile I think, is not an issue. Single dose administration has been used effectively by pediatricians for more than 13 years. But there are a couple of points that should be added to this slide that may be applicable to specific populations.

I work in an inner-city hospital; many families are dysfunctional, homeless, live in shelters. They are not able to comply with a 10-day oral regimen that requires twice a day or three times

a day administration. For me, it's an important availability of a parenteral agent that I feel comfortable with, to give them the drug in a single dose.

In addition, there will be some children who you are less comfortable with about otitis media; who are running high fever. You're concerned about a potential that is beyond that of middle ear infection, and for those children with a high serum concentrations achieved and the high concentrations in body fluids and tissues, is a level of comfort to the physician as well.

I will stop at this point and turn to Dr. Jeffrey Blumer who will present some of the pharmacokinetics and also corroborate some of the data presented by Dr. Giebink.

DR. BLUMER: Mr. Chairman, members of the advisory panel, and honored guests, good morning. I've been asked to talk a little bit about the pharmacokinetic and pharmacodynamics of ceftriaxone as they relate to otitis media. To do that, I think it's important to understand some of the key issues that are involved in decisionmaking and therapeutic treatment of otitis media.

First of all, within the context of this

infection our treatment is empiric. Unlike many infections where it is common to culture patients and make decisions or make ultimate decisions based on those culture results, with otitis media our treatment remains empiric and therefore we need to make our best guess as to what the pathogens involved are, and take our best guess as to what the susceptibility patterns of those pathogens are, and go ahead and treat.

As Dr. Giebink alluded, there's an overall, very high, spontaneous cure rate with this illness; however, the spontaneous resolution rate varies with the pathogen, and it's the pathogen that we're most concerned about, the streptococcus pneumoniae, which is more likely to cause systemic illness, that is least likely to resolve spontaneously.

In conjunction will all this, when parents bring their children to the pediatrician or general practitioner with signs and symptoms of acute otitis media, there's a sort of an expectation that they will receive therapy, that they will receive treatment.

So that in our current environment, in our current health care environment where cost becomes a major driving force in antibiotic selection, we have a drug like amoxicillin which has been used now, for more than two decades, we understand that it's safe

and it remains three to six times less expensive than the other oral antibiotics.

And for these reasons as well as sustained effectiveness, it remains a drug to be considered for the acute, uncomplicated case. However, in this same health care environment, we have no alternative at the present time for the children who can't tolerate all medication, who come in vomiting, or whose family situation is such that they cannot complete a full course of oral therapy.

Now -- and I apologize for showing the same slide -- I think you should have had some copyright or something on this. But I think that we're certainly, in some ways indebted to Dr. Craig and his colleagues for helping synthesize the clinical, bacteriologic and mechanistic aspects of the treatment of otitis media, to help us try and understand what the determinants of success may be.

This slide, as Dr. Giebink showed you, looks at a synthesis of data referring to streptococcus pneumoniae, which are in the open symbols, and Haemophilus influenzae in the closed symbols, looking at three different classes of antibiotics: the beta-lactams, the macrolides, and trimethoprim sulfa.

On the *Y* axis is plotted bacteriologic cure,

and this is a compendium of studies from the literature. On the *X* axis is the time of the dosing interval, or percent of the dosing interval -- so obviously that varies from drug to drug -- that the concentration is above the MIC for the infecting pathogen.

This is based on plasma concentrations or serum concentrations. And what you'll see is, if you can maintain concentrations -- and this relates back to the mechanisms of actions of these drugs -- certainly for beta-lactam antibiotics we know that these are time-dependent killers. So it's time above MIC that we associate with clinical efficacy.

It appears that in otitis media, the macrolides and trimethoprim sulfa work the same way. So again, if we can maintain concentrations in the plasma and by inference, in the middle ear fluid -- because this is going to be equilibrium process of sorts -- above the MIC for about 60 percent of the dosing interval, we'll begin to approach 100 percent cure.

Now, we can look at this with respect to middle ear fluid concentrations themselves, and here we've plotted, with the same kind of grouping, bacteriologic cure versus peak middle ear fluid

concentration over MIC ratio. And once again, if we have a ratio greater than ten we can begin to approach 100 percent cure.

So this is the clinical, bacteriologic, mechanistic paradigm in which any drug being used for otitis media has to be evaluated. Now, as a pharmacologist, I think with a menu of 13 or 14 drugs to choose from, we have to have some criteria to make decisions. And I would argue that there are basically three types of determinants of effective therapy.

There are pharmacokinetic determinants, pharmacodynamic determinants, and pharmaceutic determinants. If we can identify a drug that has favorable characteristics in each of these areas we will by definition, have effective therapy. Pharmacokinetics of course, describes what the body does to the drug -- the process of absorption, distribution, metabolism, and excretion.

Pharmacodynamics deals with how the drug works, what its safety profile is, what its mechanism of action may be. Pharmaceutics is the formulation, the palatability that you've heard discussed before, the presence of inert ingredients.

Now, we can begin to look at what are the ideal qualities in each of these areas for a drug to

treat otitis media. Pharmacokinetically we're looking for a drug with a long half-life. Half-life translates directly into dosing frequency, and of course the longer the half-life, the less frequently we need to go to the drug.

We want this drug to penetrate through the site of infection -- in this case, into the middle ear -- in concentrations that will inhibit bacterial replication and ideally, to kill the bacteria. And at the same time we want to avoid any drug metabolism and we want to avoid any renal elimination by secretion as opposed to filtration because those are two sites of drug-drug interactions.

Many of the children that we're treating for otitis media today have chronic illnesses and require chronic therapy. The last thing we want to do is introduce a drug for an inner current infection that throws their bronchodilator or their anti-convulsion therapy all out of whack.

Pharmacodynamically, ideally we'd like a bactericidal agent. We'd like a drug that can go in and kill the bacteria. Many of the patients that we're treating today are either absolutely or relatively immune compromised; however, in immune-competent patients this is probably less important

that the beta-lactamase stable.

Beta-lactamase remains one of the most important mechanisms of resistance and therefore we want to select among those drugs that are stable to this particular degradation pathway.

And of course, we want these drugs to be safe. Safety has to be defined not only in terms of an absence of major organ system side effects, but also we want a drug that has a low incidence of rash and gastrointestinal side effects. None of us like mothers bringing in big garbage bags full of diapers into our offices and say, see what you did. So this is something that has to be considered as we're making drug selection.

Pharmaceutically, we'd like these drugs to be available in liquid formulations. We need pediatric formulations and we're fortunate today that most of the drugs that were discussed previously, indeed are available in pediatric formulations. But they must be palatable to young children. Palatability is one of the major determinants of compliance in our patient population, and this is one area where we have a lot of conflict between parents and their children.

The drugs also have to be able to be given

with food and unfortunately, this where data is lacking. I don't know of any data that tells us about the effects of Happy Meals or Fruit Loops on the bioavailability of any of the antibiotics that we use.

And finally, we need a dosing regime that assures compliance, and in 1997 and for the foreseeable future, that means once or twice a day dosing.

Now, because we're going to focus on a parenteral agent today, the pharmaceutical aspects of this become much less important. But I think as we evaluate drugs in general, this is a major paradigm.

Now, moving to ceftriaxone, the subject of our discussion, this is a drug that we're very familiar with. We have about 13 years of experience with this in pediatric patients, treating both moderate to severe infections. It is currently one of the drugs of choice for treating bacterial meningitis, and has had extensive use in the outpatient department in the management of presumed bacteremia in infancy.

Despite this relatively extensive use over a long period of time, we've seen little resistance developed to this drug, and I think that's been of value.

I'd like to now look at the pharmacokinetic

and pharmacodynamic aspects of this drug as they relate to otitis media. Certainly, ceftriaxone has a unique pharmacokinetic profile and this does predict its effectiveness in treating acute otitis media.

I think this is best shown in a study that's been recently conducted in Iceland where a group of about 48 patients who were undergoing tympanotomy tube replacement were given a single, intramuscular dose of 50 mg/kg of ceftriaxone, and then they had serum and middle ear fluid samples taken at varying times after the dose -- up to 48 hours.

What you can see here is, the serum levels are quite high and showing elimination half-life of about six hours -- and I'll show you that in a moment. The middle ear fluid levels seem to peak in about a day, and the half-life in the middle ear fluid based on this slope seems to be much longer.

In fact, if we look at these pharmacokinetic parameters in this patient group, you'll see that the peak plasma concentration is 171; however, the peak middle ear fluid concentration is 35. If you reflect that concentration back to some of the MIC values that we've heard earlier, where resistant pneumococci have MIC_{90}s of about 1 microgram/ml, you can see that we exceed that handily.

The time to peak is about an hour-and-a-half after the IM dose in the plasma, and 24 hours after the IM dose in middle ear fluid, and the half-life in serum is six hours in contrast to 25 hours in middle ear fluid.

To synthesize this kind of data together we can reproduce this middle ear fluid concentration time curve and extrapolate it out to seven days based on the pharmacokinetic pattern -- the first order elimination that we'd expect for this drug.

And we can see that for penicillin susceptible pneumococcus, Haemophilus influenzae, Moraxella catarrhalis, we've maintained concentrations in the middle ear fluid, above the MIC for somewhere between six and seven days, and even for the resistant or non-susceptible strains of streptococcus pneumoniae, we've maintained concentrations above that for about four or five days.

Now, when we integrate this kind of data with what we know about the killing mechanism of ceftriaxone -- and these are ceftriaxone killing curves that are generated with concentrations that are twice, four times, and eight times the MIC. So for the most resistant organism it would be somewhere between 8 and 16 micrograms/ml.

You can see that indeed, ceftriaxone is a time-dependent killer -- it's irrespective of dose. Remember that at about an hour-and-a-half we get middle ear fluid concentrations that begin to approach these MICs and exceed it, and it looks as though by 12 hours we've had at least a 3-log kill of organisms. So even before we've peaked in the middle ear fluid, we could expect to have a 3-log kill of the organisms present in there.

When you look at this then, in terms of the pathogens that are involved -- and again, here are the MICs for penicillin susceptible, intermediate, and resistant pneumococci, Haemophilus influenzae, and Moraxella catarrhalis -- the maximum middle ear fluid concentration to MIC ratio, which we again thought needed to be greater than ten, is indeed much greater than ten for all of these -- at worst, three-and-a-half times greater -- and at the time above the MIC exceeds 100 hours for all of these organisms.

Moving to pharmacodynamics, we know that ceftriaxone is characterized by the potent activity against the three major pathogens that cause otitis media, and it has maintained this potency without adversely affecting microbial ecology despite its widespread use, both in inpatient and outpatient

settings.

Now, over the years -- and this is data from 1987 through 1996 for a number of pathogens -- I think it's important that as with other beta-lactam antibiotics, there has been gradual, sort of MIC-creep, if you will -- gradual changes in MIC -- but even today, the MICs for pneumococcus and for these other organisms, are well below the concentrations that we expect to achieve in any body cavity with currently recommended doses of ceftriaxone.

I've included the data for Neisseria meningitis on this slide because one of the concerns that we all have is that this is a drug that we commonly use for bacterial meningitis. It would certainly appear that both pneumococcus and meningococcus have retained their susceptibility to ceftriaxone and would be expected to continue to be effectively treated with this drug, even in current circumstances.

The same kind of information is available for gram-negative enterics, although I don't have a slide to show you. It's very clear that the MICs have been relatively stable for most of the gram-negative enteric organisms throughout this same time period.

Now, looking at activity against

pneumococcal isolates, a majority of which were middle ear fluid isolates, these are relatively current data from three different studies looking at penicillin susceptible, penicillin intermediate, and penicillin resistant pneumococci.

These ceftriaxone and MICs again, seem to peak out at one to two, and we heard this morning that the expectation is that it's not likely that we're going to see these organisms have MICs much greater than eight.

And in fact, in talking to my colleague Dr. Jacobs, it appears that this range of MICs is the very same range he saw back in South Africa when he first identified these penicillin resistant pneumococci back in the late 1970s.

So there seems to be some stability in the prediction that we're not going to get MICs of 100 and 1,000 seem to be holding true, at least at the moment.

Well, what about this issue of resistance, because obviously, that's a concern that we all have, and it is indeed a global issue. It is not an issue related to a single drug and in fact, we cannot relate the resistance we're seeing in the environment to any single drug or its introduction.

It's certainly a natural phenomenon that can

be intrinsic to the organism or it can develop through mutation. Clearly, this is a complex, scientific phenomenon that has to do, not only with the environment which the organism are growing, but the kinds of selection pressure that we may exert through our use of antibiotics.

However this occurs, it has clinical implications, and these clinical implications are important because it requires that we take these changes in antimicrobial susceptibility into account as we prescribe antibiotics.

At the present time, all three of the pathogens that we associate as major pathogens causing otitis media show resistance. There is beta-lactamase production among Haemophilus influenzae and Moraxella catarrhalis and Dr. Giebink showed you. We see the penicillin resistance due to altered penicillin binding proteins among streptococcus pneumoniae.

However, this resistance is exacerbated by some of the things that we do routinely. It's exacerbated when we use ineffective antibiotics; it's exacerbated by poor compliance practices; and it's exacerbated by the presence of sub-inhibitory concentrations that may be present during inadequate troughs with all therapy where we're giving more than

one dose a day.

This selection process is obviously, influenced by the MIC of the organism or its susceptibility, the pharmacokinetics that we discussed. So that in vitro, sub-inhibitory concentrations can lead to the emergence of resistance. In vivo, what we see are resistant organisms emerge in the presence of sub-inhibitory troughs.

So that given this paradigm it would appear more likely that short-term exposure to a highly potent antibiotic is less likely to select for this resistant than the intermittent exposures that we see with all therapy. And obviously, this is going to be exacerbated by the poor compliance that's often typical of clinical settings.

Now, is there any data to suggest that this is in fact, true, and how does this roll itself out? And there's a variety of different sources we can draw on to begin to put this together.

We have some experience that shows some contrasts at least, that may provide a lesson for us. here we have penicillin resistant, pneumococcal patterns in Europe where there appears to be a correlation between antibiotic use and the mode of

administration in particular, and the emergence of penicillin resistance.

So when we look at countries that have very high levels of resistance, those like Spain and France, they have massive use of oral antibiotics, very poor treatment compliance, and high level use of, particularly oral cephalosporins, and to a lesser extent, oral penicillin.

In contrast, we have a country like Italy, very close neighbor to these two, where there a very low incidence of penicillin resistant pneumococcus. Here they have a relatively, much lower use of oral antibiotics. They tend to favor the use of injectable antibiotics for things that we would often never even consider injectable antibiotics -- in particular, the third generation cephalosporins. So that's one correlation.

One of the other things that's been done -- and this is a study that you'll see shown in several ways -- but one of the studies that was performed in looking at otitis media was a study comparing ceftriaxone and amoxicillin/clavulanate, and I'd like to discuss one aspect of it with you.

This was a randomized, comparative trial comparing these two drugs -- that is, a single, 50

mg/kg dose of ceftriaxone versus ten days of amoxicillin/clavulanate -- performed by Dr. Cohen and his colleagues in France.

It's important to recognize that the dose of amoxicillin/clavulanate here is twice the dose that we recommend in the United States. So they were using 80 mg/kg of amoxicillin per day.

And as part of this study, otitis media was diagnosed based on the signs and symptoms that Dr. Klein shared with you using Dr. Paradise's paradigm that from the group in Pittsburgh. And these patients has nasopharyngeal swabs taken before and after therapy.

So you can see there were 247 patients in the ceftriaxone group; 250 patients in the amoxicillin group. They received their therapy and then ten days after the start of therapy they had another swab taken. So for the ceftriaxone group that was ten days after their shot; for the amoxicillin/clavulanate group that could have been on the last day of therapy or at most, two days later.

What you can see with this is, from the three major pathogens, was that amoxicillin/clavulanate was much more effective, or apparently so, in decreasing the rate of colonization,

both for pneumococcus and Moraxella catarrhalis. But remember the difference in time between treatment and taking this last swab.

However, when you look in particular, at the makeup of these bacterial populations, there's certain things that do show up. There were no differences between the before and after treatment makeup of the Haemophilus influenzae population or the Moraxella catarrhalis population. But among the pneumococcal populations it was very clear that there was a relative enrichment in penicillin non-susceptible strains after amoxicillin/clavulanate treatment compared to ceftriaxone treatment.

Nevertheless, when we try and say, well what impact did this have on patients, the answer was I think somewhat reassuring. And that is, that even after therapy there were no more patients that had resistant organism they were carrying than prior to the start of therapy. So we didn't suddenly see a group of patients come on the scene who now are carrying more resistant organisms.

Again, we have to take into account the difference between the time that therapy was stopped and the time these samples were taken in the two groups, but we certainly don't see any increase in the

number of children carrying resistant organisms.

Lastly, one of the concerns that we do have is that this is a drug that's sometimes used for serious infection, and of course the place that we see serious infections have their origins in many cases is the gut. So what impact does this kind of therapy have on gut flora?

And it's very clear, first of all, that ceftriaxone has no impact on anaerobic flora in the gut, and that's been looked at in a number of cases. Among those patients who have measurable concentrations of ceftriaxone in their stool after an IM dose, and that's roughly 50 percent of patients, it's very clear that the aerobic flora is eradicated very quickly -- within 24 hours -- and with that eradication we see an increase enrichment in Candida and enterococci.

However, with continued therapy with ceftriaxone -- and unfortunately we don't have any data where ceftriaxone was stopped after the first dose and no more were given -- but with continued therapy where this has been looked at, by day 3-10, the recovery of normal flora has re-established itself.

And even though there are resistant

organisms present for a week after the end of therapy, by two weeks after the end of therapy, the pre-therapy susceptibility pattern has re-established itself. So there appears to be no long-lasting impact on GI flora associated with ceftriaxone use as well.

We've heard a lot of discussion this morning about resistance, and obviously that's a major concern of ours, but as a pediatrician I'm also concerned that we don't lose sight of the fact that there is not -- that treatment failure is in fact, not synonymous with resistance; that there are other factors that come into play.

And I think this was best illustrated by a study reported from Rochester by Michael Pichichero and his Elmwood Pediatrics Group which is a private practice group in Rochester. They looked at a group of children who are coming for their very first episode of otitis media, and they did tympanocentesis, and compared that to a group of patients who had either persistent disease, disease that hadn't resolved, or patients who had either three episodes in six months or four episodes in a year.

The results are very interesting. First of all, the bacteriology is very much the same so the rank order of pathogens that they saw didn't change

whether it was their first episode, or their second, or third, or fifth, or umpteenth episode.

There was however, a relative enrichment in resistant organisms in these patients with persistent or recurrent disease. So more penicillin resistant pneumococci, more beta-lactamase producing, Haemophilus influenzae, etc. And it would be hard to tell with Moraxella since virtually all of them are beta-lactamase producers.

Nevertheless, what they showed was that oral -- in their practice they were seeing a treatment failure rate approaching 20 percent, and this was a treatment failure rate with amoxicillin. Nevertheless, most of the middle ear organisms that they cultured in patients who failed, were susceptible to the original antibiotic prescribed.

I think that's an important finding because that tells us something about other factors that have to be considered. There are clearly other biologic issues that we need to learn about in order to fully understand why some children respond and other children don't respond to an antibiotic therapy that we would expect to be effective.

The other thing that's important is -- it's certainly in Cleveland and apparently in Rochester and

other places -- it is not uncommon to say if a child didn't respond to ten days of therapy with amoxicillin we went ahead and gave them another ten days of therapy. And this too, was tried in this Rochester study with less than a 30 percent response rate.

So it appeared on this basis, that successful treatment with an antibiotic requires two things. It required that we have activity against beta-lactamase producing organisms, and it required that we achieve concentrations in the middle ear fluid that would be effective against all the likely pneumococcal pathogens that we would find.

So how did ceftriaxone fit in with all this resistance paradigm that we've discussed this morning? Well, it is quickly bactericidal in the middle ear fluid, even for resistant pathogens; complete compliance with therapy is assured because we see this after a single dose.

We don't achieve any of these sub-bactericidal trough concentrations, however, we do have persistent bactericidal concentrations in the middle ear for a number of days after the first dose. And therefore, we're in a situation where we're less likely to see selection of resistant strains.

Just to reiterate this, reproducing again,

that middle ear fluid concentration versus time curve, again, the time above the MIC seems to be linked to bacteriologic efficacy and we have that versus virtually all of the pathogens we're likely to see.

And when we combine that data with the killing, it's likely that even before the drug has fully peaked in the middle ear fluid that we will see more than a 3-log kill; such that even when the drug concentration in that department falls below the MICs, there won't be any organisms left there to select for resistance. And we're not going to achieve sub-inhibitory concentrations at a time when there are any organisms left.

To compare and contrast ceftriaxone -- the mode of therapy being proposed -- to what we see with oral agents, we have a drug, ceftriaxone, that's effective against all three of primary pathogens, where as you heard, some of the oral agents have a varying activity here.

It is beta-lactamase stable which is not true for all of the oral agents, and certainly effective against many of the resistant pneumococcal isolates. It requires only a single dose compared to multiple doses of oral agents.

And compliance because of this single dose

therapy is assured, whereas compliance is variable with oral agents depending on the number of doses and days of therapy that's required to cure the patient, as well as the ability of families to actually get the drug.

We're not going to be troubled by sub-inhibitory concentrations of drug, and the exposure of GI flora is short, whereas it's very prolonged with our oral therapy.

So to bring this back in conclusion, to the pharmacokinetic, pharmacodynamic, and pharmaceutic paradigm that we started this discussion with, it's very clear that ceftriaxone fulfills all the pharmacokinetic characteristics we were looking for, all of the pharmacodynamic characteristics we were looking for, and those pharmaceutic characteristics that could be pertinent to a drug that can be administered parenterally.

I'd like to finish here and turn over the discussion to Dr. Jonathan Solsky who will present some of the clinical trials data in support of this SNDA. Thank you.

CHAIRMAN CRAIG: I'd like to remind the sponsor there is about 17 left of your time.

DR. SOLSKY: Good morning. Today I will

present the data from our clinical and bacteriology trials that demonstrate clearly the favorable efficacy and safety of a single dose ceftriaxone, given as an IM injection in the treatment of acute otitis media in children.

In total, our database consists of 2,450 patients; 1,350 of whom received ceftriaxone. Thus, this supplemental NDA represents one of the largest databases on this indication presented to the Anti-Infective Advisory Committee.

The rationale for the clinical development program for Rocephin™ in this indication, was based on a clear need for parenteral therapy in the treatment of acute otitis media. Examples of this may include infants and children unable to tolerate oral therapy, patients at risk of pneumococcal infection, as well as addressing the problematic issue of lack of compliance resulting in misuse with multi-dose, multi-day, oral therapy.

In vitro and in vivo trials clearly show that the superior bactericidal activity against the three major causative pathogens of AOM. Due to its unique pharmacokinetic properties, sustained high concentrations are achieved in the middle ear fluid, effectively exceed the MIC_{90}s for even resistant

pathogens for several days.

Thirteen years of use has demonstrated its excellent safety profile in the pediatric population. Furthermore, a single dose of IM Rocephin™ assures guaranteed, full course treatment and compliance.

Our clinical development program consisted of two bacteriology studies and four clinical studies in the U.S. Of these six trials, one of the bacteriology studies and three of the clinical studies were investigator-initiated. The remaining two were Roche-sponsored, multi-center trials. Supportive data comes from one multi-center study conducted in France and the pharmacokinetic study that Dr. Blumer has presented the data from.

I'd like to now turn to the two bacteriology studies. These studies demonstrate that ceftriaxone exhibits bactericidal activity against the three major pathogens of acute otitis media. Furthermore, effectiveness against penicillin-resistant strep pneumoniae and beta-lactamase producing strains of H. influenzae and M. catarrhalis, were observed.

The comparative bacteriology study was an open-label, randomized study conducted by Dr. Howie in Galveston, Texas, between 1991 and 1994. The study was primarily designed to evaluate the bacteriologic

etiology and bactericidal efficacy of a single dose of Rocephin™ given at 50 mg/kg up to one gram, in comparison to a combination regime of CR-bicillin, single shot given IM, followed by a 10-day course of trimethoprim sulfa given orally.

As part of the unique double-tap study design, tympanocentesis was performed in all patients, not only at baseline but also at day-2 to 3. Patients were enrolled with the diagnose of acute otitis media between the ages of six months to three years. The primary efficacy outcome was bacteriologic eradication at day-2 to 3.

Two-hundred-and-three patients were enrolled in this trial; 154 receiving ceftriaxone and 49 receiving the comparator. At baseline, the results of the tympanocentesis culture revealed that 84 of the 154 patients who received ceftriaxone had one of the three major pathogens of AOM.

In the ceftriaxone group, the repeat tap done at day-2 to 3 revealed 100 percent eradication of strep pneumoniae, Haemophilus influenzae, and Moraxella catarrhalis, including beta-lactamase positive strains.

On the repeat tympanocentesis done at day-2 to 3, four additional patients on ceftriaxone had new

isolates grow out on culture. Thus, of the 87 patients on ceftriaxone assessed at day-2 to 3, 95.4 percent had bacteriologic cure.

Of the four patients who had bacteriologic failure, none of them had persistence of the baseline pathogen. Of the four bacteriologic failures in the ceftriaxone group, three were new infections at day-2 to 3, not present at baseline of M. catarrhalis. In the fourth case the patient had H. influenzae and strep pneumoniae isolated at baseline, which was eradicated at day-2 to 3, and now had a super infection of M. catarrhalis.

After consultation with the FDA we initiated a second bacteriology study that was more geographically diverse to augment the bacteriology data that we had already collected. This study was an open-label, prospective, non-comparative trial of single dose ceftriaxone given at 50 mg/kg up to one gram IM, conducted at six centers in 1996.

Tympanocentesis was to be performed at baseline in all patients and as indicted in the protocol, had to be repeated if the patient was assessed to be a clinical failure. Children from six months to six years of age were enrolled in this trial, who had a diagnosis of acute otitis media.

The primary efficacy outcome was presumed bacteriologic eradication based on clinical outcome at week-2. At baseline, 79 of the 108 patient enrolled had 100 isolates grow out on culture. The distribution of baseline pathogens was 43 percent step pneumoniae, 39 percent Haemophilus influenzae, and 18 percent Moraxella catarrhalis.

Approximately 23 percent of the strep pneumoniae was penicillin-resistant, while 40 percent of Haemophilus influenzae was beta-lactamase positive, and virtually all of the Moraxella catarrhalis was beta-lactamase positive.

At week-2, of the 79 patients with pathogens isolated at baseline, 82.3 percent were found to have a cure; that is, complete resolution of signs and symptoms of acute otitis media. The presumed, microbiologic eradication of the baseline pathogens based on clinical outcome, shows cure rates of 81.4 percent of strep pneumoniae, 82.1 percent for Haemophilus influenzae, and 66.7 percent for Moraxella catarrhalis.

For the penicillin resistant and penicillin susceptible strains of strep pneumoniae, presumed eradication rates of 60 percent and 87.9 percent were observed. For the beta-lactamase positive strains of

Haemophilus influenzae, 83.3 percent presumed eradication was seen. And for beta-lactamase positive strains of Moraxella catarrhalis, 64.7 percent.

In summary, of the 79 patients with baseline isolates, overall, 82.3 percent were presumed bacteriologically eradicated based on clinical outcome at week-2. At the end of this 4-week study 36 patients were assessed as clinical failures, and as stipulated in the protocol, were to have a repeat tap done.

However, only four of the 36 patients actually had a follow-up tap. This reflects the realities of clinical practice. And major reasons for why these taps were not done was, in the vast majority of cases, the parents refused to have a second procedure implemented, or in the physician's opinion, a repeat tap was not warranted given the clinical assessment of the child.

Of note, in all four cases where follow-up taps were performed, the baseline pathogen of strep pneumoniae, penicillin susceptible, was 100 percent eradicated.

The results from these two bacteriology studies in conclusion, confirmed the ceftriaxone efficacy against the three major causative pathogens

of acute otitis media. I'd like to now present the clinical efficacy results from the five clinical trials.

Analyses of these five trials consistently indicate overall, comparable efficacy to a variety of the most commonly used antibiotics for the treatment of acute otitis media. The four U.S. studies in the clinical program compared the efficacy and safety of Rocephin™ administered at 50 mg/kg as a single dose, versus oral therapy given two to three times a day for ten days.

A total of 1,579 patients were enrolled in these four U.S. studies. The studies were all similar in design, being prospective, randomized, investigative blind, and in the case of Dr. Green's amoxicillin trial, double-blind, double-dummy.

Age range for enrollment was similar and approximately in all the trials, overlapped from three months to six years of age. Efficacy assessments again, were similar at two and four weeks.

Additionally, a supportive trial conducted in France, confirmed the efficacy and safety of ceftriaxone in acute otitis media. This trial also studied a single dose of ceftriaxone at 50 mg/kg up to a maximum of one gram, given IM as a single dose

versus amoxicillin.

As you can see here, the dose of amoxycillin is twice what it is recommended in the United States. This is the recommended dose in France and reflects France's high incidence of penicillin resistant pneumococci.

Five-hundred-and-thirteen patients were enrolled in this trial, and the trial was very similar to our U.S. studies, being prospective, randomized, multi-center, although open-label. Age range for this trial was four months to 2.5 years, and efficacy assessments again, were at two and four weeks.

All five trials had similar inclusion criteria. The diagnosis of acute otitis media in all of these trials was based on the presence of middle ear effusion associated with signs or symptoms of an acute illness.

Pneumatic otoscopy was performed to document tympanic membrane abnormalities and lack of mobility. Tympanometry and in the case of Dr. Klein's trimethoprim sulfa trial, acoustic reflectometry was done to corroborate the findings of middle ear effusion.

The two analysis populations were defined for all these studies as being the intent-to-treat and

standard. The intent-to-treat includes all patients who receive drugs. The standard population excludes from the intent-to-treat, those patients who did not have signs or symptoms of acute otitis media, who received other antibiotics due to illnesses unrelated to acute otitis, missed the primary endpoint assessment and was thus a partial exclusion, or lost to follow-up, or received a second dose of ceftriaxone.

For the U.S. studies, cure is defined by IDSA guidelines and FDA points to consider were used. Cure was defined as complete resolution of signs and symptoms exclusive of effusion. Failure, conversely, was defined as a lack of complete resolution of signs and symptoms exclusive of effusion.

In all the studies, the protocols defined day-10 or week-2 as the primary endpoint. Both the intent-to-treat and standard populations assessed as cured, only patients completely free of signs and symptoms of acute otitis media. All other patients, including those that were considered to be improved at the primary assessment point, were rigorously assessed as a failure in these trials. All failures were carried forwards.

In the French study, the primary efficacy

parameter was clinical success, which was defined as clinical cure plus improvements. The cure rate being presented today for the French study was calculated to be consistent with the analyses done in the U.S. study.

The statistical analysis used was the method recommended by the FDA for this indication. That is, a test equivalence done by using a 2-sided, 95 percent confidence interval for the difference in cure rate between ceftriaxone and comparator, must be within the prespecified limits and include zero.

This table summarizes the results of the clinical evaluation for the cure rate at the primary, clinical endpoint based on the intent-to-treat population. In the U.S. studies the cure rates for ceftriaxone ranged from 41.5 percent to 85.2 percent. In the comparator arm, cure rates ranged from 34.4 percent to 85.0 percent. Cure rates in France for both ceftriaxone and comparator were similar at 62.4 percent.

It should be noted that in the cefaclor study, the low cure rates for both ceftriaxone and cefaclor are due to the time point at which the primary assessment was conducted. Unlike the other trials where assessments were made approximately two

weeks after the initiation of therapy, in the cefaclor study clinical outcome was only assessed as per protocol, at the second follow-up visit which was to occur three weeks after the initiation of therapy.

However, treatment actually occurred 14 to 197 days after the initiation of therapy with a median of 40 days after the initiation of therapy. Thus, this low cure rate in this cefaclor study is more reflective of a week-4 assessment with all the attendant issues confounding outcome at week-4.

The overall equivalent results of each of these studies, based on a 2-sided, 95 percent confidence interval for treatment difference of cure rates at the primary assessment point for the intent-to-treat population, is graphically displayed on this line.

In the U.S. studies, statistical equivalence can be seen for the trimethoprim sulfa trial, amoxicillin, and cefaclor studies. In the amoxicillin/clavulanate trial the 95 percent confidence interval for the difference between ceftriaxone and comparator, fits within the pre-specified limits; however, does not include zero by only .8 percent.

To put this in context, if one had three

additional more patients, up to 649 who were enrolled, who were assessed as a cure, this would also be an equivalent statistical trial. In addition, in the amoxicillin/clavulanate trial -- which if you recall, studied twice the dose of amoxicillin that's done in the U.S. -- clearly equivalence is seen from a statistical standpoint.

In the standard population analysis, quantitatively higher cure rates were calculated. Similar statistical equivalence of treatment groups are seen in standard population analysis as in the intent-to-treat. And for a lack of time, I will move over those and summarize.

And the comparative clinical trials consistently demonstrate that a single dose of Rocephin™ IM exhibits efficacy comparable to a standard 10-day multiple, oral dose treatment for acute otitis media.

I'll quickly move through our safety section. The following section reflects a safety database of 1,890 patients who were enrolled in the six U.S. studies, of which 1,048 patients received ceftriaxone. The data from these six U.S. studies confirmed that a single dose of ceftriaxone IM is well-tolerated and safe.

The integrated U.S. safety database comprises an equal distribution of males and females with a mean age of 24.9 months, with a range of 3 to 83 months, and a racial distribution of 60 percent white, 22 percent black, and 17 percent other racial groups.

In terms of potentially-related, adverse events, 23.6 percent of all U.S. patients receiving ceftriaxone reported an adverse event. In the comparative trials, patients on ceftriaxone reported potentially-related adverse events from 12.3 percent to 31.1 percent.

In the comparator group, patients who reported adverse events from 12 percent to 55.7 percent. Overall, patients on ceftriaxone had a reporting incidence of adverse events similar to patients receiving comparator agents.

The most frequently reported, potentially related, adverse events in children in the U.S. receiving ceftriaxone, were diarrhea, diaper rash, rash, injection site pain, and vomiting. While diarrhea was the most frequently reported adverse event on ceftriaxone, diarrhea was also frequently reported for amoxicillin, trimethoprim sulfa, and amoxicillin/clav, with an incident of 5.3 percent, 8

percent, and 45.6 percent, respectively.

This slide summarizes the percentage of patients who were withdrawn from therapy due to an adverse event. Overall, 2.3 percent of children had to be prematurely discontinued from oral therapy due to an AE. The most frequently reported adverse events with oral therapy were: diarrhea, rash, and vomiting with amoxicillin/clavulanate; rash and vomiting with amoxicillin; and rash with trimethoprim sulfa.

Six ceftriaxone-treated patients experienced serious adverse events. All of these patients recovered and five of these cases were considered by the investigators to be unrelated. One case that was considered remotely related was a febrile seizure with no sequelae once the patient's fever depervesced.

Seven serious, adverse events occurred on comparator agents -- six unrelated. The one probably related case was of erythema multiform on cefaclor. No deaths were reported in any of these trials.

In summary, the integrated safety database consists of 1,048 patients who received ceftriaxone in U.S. trials, reporting no unusual or unexpected adverse events. The well-established safety profile of ceftriaxone was confirmed in these trials.

I'd like to briefly report on the parenteral

survey data.

CHAIRMAN CRAIG: Very briefly.

DR. SOLSKY: Okay -- in two of the studies. In this double-blind, double-dummy study of amoxicillin, of those patients who responded, 67.1 percent preferred parenteral therapy, and one can see that in a ratio of 6:1, patients preferred injection over oral therapy.

In the amoxicillin/clavulanate trial at week-2, not only were the vast majority of patients whose children received ceftriaxone, satisfied with the route of administration, but furthermore, 90 percent of those parents would choose the same treatment in the future.

On the other hand, 75 percent of parents whose children received oral therapy, would prefer their child to receive in the future, an IM injection.

I'd like to summarize what you have heard today -- very quickly.

(Laughter.)

Single dose, IM Rocephin™ for the treatment of acute otitis media offered favorable pharmacokinetics, pharmacodynamic, and pharmaceutics. It has demonstrated a long serum half-life in infants and children with bactericidal serum levels reached

within 90 minutes of administration.

Its unique pharmacokinetic profile results in sustained, high concentrations in the middle ear fluid, exceeding the MIC_{90}s of three major pathogens for several days. It has none of the pharmaceutical issues of oral suspension antibiotics.

Bactericidal activity has been demonstrated against the three major pathogens. It demonstrated bactericidal activity in vitro against strep pneumoniae, including penicillin resistant strains. It has excellent in vitro activity against H. influenzae and M. catarrhalis including beta-lactamase positive strains.

Bactericidal eradication of resistant pneumococci has been demonstrated in experimental otitis media in animals. Furthermore, bactericidal eradication has been confirmed on clinical, bacteriologic studies.

The possibility of increasing resistance is minimized due to the unique pharmacokinetic properties, sustained duration of bactericidal activity, and parenteral administration. Stepwise exposure of bacteria to sub-inhibitory, antibiotic concentrations which may occur with oral, multiple dose agents, especially when one is non-compliant, is

negated with a single dose of Rocephin™.

Epidemiological data from Europe is suggestive that parenteral therapy in outpatients is associated with a lower incidence of resistance. Ceftriaxone has remained clinically effective in the changing environment of microbial resistance. Efficacy has been demonstrated in comparison to standard treatment. One dose clearly exhibits efficacy comparable to standard, 10-day, multiple oral dose therapy.

We have shown over 13 years, a well established safety profile with no unexpected or unusual adverse events reported in our clinical or bacteriology trials in patients treated with acute otitis media.

There are advantages of single dose, parenteral therapy. It eliminates the issues of refrigeration, inaccurate dosing, difficulty in swallowing, variable absorption oral agents. Although transient injection site pain does occur, Rocephin™ obviates difficulties in administering to infants and children, multiple dose, multiple day, oral therapy.

A single dose of IM Rocephin™ assures guaranteed, 100 percent full course treatment and compliance. Inadequate compliance is common and

problematic with standard multidose oral therapy, potentially leading to lack of efficacy or possibly, resistance.

It effectively eliminates concerns whether prescription drugs are filled, doses are missed, or misuse of unused drugs. Parenteral preference for single dose IM therapy has been shown in our two surveys. Single dose IM Rocephin™ offers the physician a valuable treatment option -- to provide optimal therapy on an individual basis to children with acute otitis media.

Those children who may not be able to tolerate oral therapy, for increased risk of pneumococcal infection, and who may not be compliant, are representative of the clinical situation where the option of single dose treatment with Rocephin™ should be available.

Rocephin™ offers a significant addition to the armamentarium for the treatment of acute otitis media. Thank you.

CHAIRMAN CRAIG: Thank you. We'll take a break right now and it will be precisely 15 minutes. We will start immediately at 10:45.

(Whereupon, the foregoing matter went off the record at 9:34 a.m. and went back on

the record at 10:46 a.m.)

CHAIRMAN CRAIG: We're ready to start again. The next part of the program is the FDA presentation, which will be done by Dr. Viraraghavan, one of the medical officers.

MR. VIRARAGHAVAN: Good morning. I'm Roopa Viraraghavan, one of the medical officers in the Division of Anti-Infectives. I reviewed Rocephin™ ceftriaxone for otitis media, and what I present to you today is the FDA viewpoint.

Broadly, this outline shows the gist of my talk, which is the NDA supplement for Rocephin™, issues in reviewing the supplement, and questions for the committee.

Currently, all anti-infective agents approved for acute otitis media are all therapies and nothing parenteral is approved. Although the majority of agents are approved for ten days, there is one oral agent that is approved for 5-day treatment of acute otitis media.

Ceftriaxone is a cephalosporin antibiotic. Its serum half-life is approximately 6.4 hours and there's activity in vitro against gram-positive and gram-negative organisms commonly infecting patients with otitis media.

As you can see, the FDA has already approved the following long list of indications. So this is the proposed labeling, and this is the addition. Acute, bacterial otitis media caused by strep pneumo, including penicillin resistant strains, Haemophilus influenzae, beta-lactamase positive and negative strains, and Moraxella catarrhalis.

The proposed dosage reads, for the treatment of acute bacterial otitis media a single IM dose of 50 mg/kg not to exceed one gram, is recommended.

The data submitted in this supplement were as follows: eight trials, one PK, five clinical, and two bacteriologic -- as we have already heard. And I will start by discussing the one Icelandic PK study, and I will follow this with the five clinical trials where I will briefly talk about two single investigative trials -- mainly the Green and Chamberlain -- and then I will follow it up with the larger, two clinical trials -- Roche clinical, French and Klein study. I will then subsequently discuss the two bacti studies.

So this is the Icelandic PK study. It had 48 patients enrolled, of which 42 were evaluable for efficacy. In this study, children with otitis were dosed with IM ceftriaxone and plasma and middle ear

samples were obtained at various time points.

The middle ear concentration levels are shown here as closed circles, and the open circles are the plasma levels. What I'd like to focus you on is the level at 1.5 hours. The level at 1.5 hours is 4 micrograms/ml. The peak level in the middle ear is at 24 hours, and that's 35 micrograms/ml. At 48 hours it's 19 micrograms/ml.

Again, the estimated half-life in the middle ear is 25 hours. The time the MICs are exceeded, as we've heard already is up to six days, as determined from simulation. So that was the PK data in a nutshell, and at this point let's move on to the five clinical trials.

None of these trials were designed with tympanocentesis. One was conducted by Roche under the U.S. IND, and herein I will describe this as the Roche clinical study. There were three, single investigative trials performed in the U.S., and one multicentered, French trial here known as the French study.

Of these five clinical trials, I will briefly talk about the single investigative trials, namely Green and Chamberlain, but then will focus on the three other clinical trials -- Roche clinical,

French, and the Klein study -- because of certain protocol issues which I will bring up.

So the Green study had 261 patients who were randomized, double-blind, double-dummy study, and the comparator was amoxicillin. Of these 261 patients, 210 were FDA evaluable and 21 were sponsor not evaluable because of loss to follow-up and intercurrent illness.

Additionally, to those 21 patients, 30 additional patients were FDA not evaluable: 25 did not have signs and symptoms of acute otitis media and five had recurrent otitis media.

So here are the results for the Green clinical study. Clinical success, day-10: 90 percent for ceftriaxone; 95 percent for amoxicillin. And the confidence intervals are -13 to 2.7. On day-30, the clinical success was 71 percent for ceftriaxone, 79 percent for amoxicillin, and the confidence intervals were -20 to 4.5.

These were the study design issues. Exclusion criteria was addled in the FDA analysis for standardization cross studies. Although this was a prospective study, retrospective evaluations were completed on day-10 and day-30. Day-10 results were obtained by questioning patients on day-14, and day-

30 results were obtained by questioning patients on day-60.

There were significant issues with the inclusion criteria. In this study, discoloration, opacity, and bulging were the terms used on otoscopic examination, and were without other inclusive criteria on the very scant, case record forms.

The important information I want to have you bring away is that only 41 percent of patients had the otoscopic finding of bulging. Additionally, although 100 percent of patients had positive tympanometry -- they had included all of these as of normal -- low compliance, high pressure and low pressure were considered abnormal tympanometry.

So now to the Chamberlain clinical study. This study had 73 patients, prospective, randomized, investigator blind study, and the comparator was cefaclor. Of these 73 patients, 51 were FDA evaluable, 20 were sponsor not evaluable because of loss to follow-up and negative tympanogram. In addition to these 20 patients, two more were made FDA not evaluable for recurrent otitis media.

These were the issues with this study. This was a terribly under-powered study. There were 640 patients that were planned to be enrolled; there were

only 73 patients who were enrolled at the end of the day. Blinding was lost in 30 percent of patients and investigator. The second follow-up visit was between day-14 and day-197.

Results, clinical cure, success: 57 percent for ceftriaxone, 48 percent for cefaclor. Here are the confidence intervals: -22 to 40. I made two changes in this study and the results fell out of the FDA lower bounds of the confidence limit suggesting that these results were not robust to even very small changes.

At this point I will briefly discuss these two single investigator trials. I would like to review the regulatory framework and then follow it with the three, substantial, clinical trials.

So the points to consider suggest two trials, one clinical and one micro trial. The clinical trial should be statistically adequate, well-controlled, and multi-center. Tympanocentesis need not be performed but is strongly recommended for treatment failures. There is a rigid case definition that must be met and you have to establish equivalence or superiority to an approved product.

In the micro trial, which is an open-label study, tympanocentesis is done, and the micros should

include 25 isolates with strep pneumo, 25 with H. influenzae, and 15 with M. catarrhalis.

Here are the divisional evaluability criteria. Clinically evaluable patients should have a clinical diagnosis of acute otitis media based on history, physical, pneumatic otoscopy, and tympanometry. Micro evaluable patients should have a micro diagnosis of acute otitis media obtained by tympanocentesis.

The Test-of-Cure visit should occur approximately one to two weeks after the completion of therapy. So here are the points to consider, recommendations for establishing lower bounds in therapeutic equivalency trials. For success rates for the better drug, here are the lower bounds of the confidence intervals.

So for success rates of the better drug greater than or equal to 90 percent, the lower bound of the confidence interval should be minus ten percent. For success rates of the better drug greater than or equal to -15 percent, and for success rates of the better drug greater than or equal to 70 percent, the lower bounds of the confidence interval should be -20 percent.

So the following review strategy for

ceftriaxone was used, and there were two analysis done: intent-to-treat and per protocol. And the data was examined from multiple perspectives by analyzing differences in clinical and micro-response to single dose versus traditional regimens, and the need for modification for antimicrobial regimen -- patients who had received two injections of ceftriaxone.

The FDA inclusion criteria included all enrolled patients between three months and six years of study entry. The diagnosis of otitis media using evaluability criteria symptoms -- one or more specific symptoms of otalgia, fever, ear pulling, TM signs of fullness, bulging, erythema, and the pneumatic otoscopic finding of impaired mobility.

So I'm not going to go through all of these exclusion criteria, but just to let you know that none of these were changed from those of the sponsor.

But for standardization across studies, the following additional exclusion criteria were added. Additionally, a history of recurrent otitis media as defined as four episodes per year for the last two years, or three episodes in a child who's 12 months old or under. And a history of acute otitis media within 30 days of entry into the study.

At this point, let's review the three,

individual, substantial, clinical trials where this presentation will focus. The Roche clinical study had 649 patients. In the study design it was a prospective, randomized, investigator blind, multi-center study with an age range of three months to six years. The comparator was amox/clavu augmentin by mouth for ten days, at 40 mg/kg per day, and the efficacy on points was clinical response at week-2 or study day-14, and week-4, study day-28.

So in this Roche clinical study which had 649 patients, 598 were considered FDA evaluable; 47 were considered not evaluable by the sponsor because loss to follow-up or signs and symptoms not consistent with acute otitis media. There were no additional, non-evaluable changes made to this non-evaluable category by the FDA. There were no study design issues.

Here are the results for the Roche clinical study evaluable population and week-2 and week-4. Here are cure rates for ceftriaxone and for augmentin -- low dose augmentin: 74 percent for ceftriaxone; for augmentin, 82 percent; 95 percent confidence and a -14 to -.5. Ceftriaxone, 58 percent; augmentin, 67 percent; -17.5 to -1.2. Recall again before we move on that there were no issues.

The next study is the Klein clinical study, which had 596 patients, prospective, randomized, investigator blind, single center study, age range of three months to three years. Rocephin™ was given but discretionarily in 23 additional patients, a second dose was given at day-2 to 3.

The comparator was trimethoprim sulfa by mouth for ten days at 40 mg of sulfa component per kilo per day. The efficacy parameter was clinical response at week-2 and week-4 against study day-14 and 28.

So in Klein's clinical study, there were 596 patients, 416 were FDA evaluable, 132 were sponsor not evaluable because they did not have baseline effusions, there were loss to follow-up, or signs and symptoms were not consistent with acute otitis media. In addition to this 132, 28 additional patients were considered not evaluable because of recurrent otitis media or otitis media less than 30 days prior.

These were the trial design issues. These exclusions of 28 patients were added for standardization across studies, and there were 23 patients who had received a second dose of ceftriaxone and who were considered unevaluable. This may bias the ceftriaxone cure rate since these patients had a

lower cure rate than single dose ceftriaxone patients. Therefore, they were entered in the standard analysis as treatment failures.

So when viewing these results, those were the issues: the 28 patients who were considered not evaluable for standardization of exclusion criteria and the 23 patients, second dose ceftriaxone patients who were treated as treatment failures.

Efficacy parameter, week-2, ceftriaxone cure rate, 54 percent; cure rate, trimethoprim sulfa, 60 percent; 95 percent confidence interval; -16 to 3.6. Week-4 cure rate ceftriaxone, 35 percent; cure rate, trimethoprim sulfa, 45 percent; 95 percent confidence interval; -19.9 to -.003.

Moving to the French clinical study, 513 patients. This study, with prospective, randomized, open, parallel group, multi-center study with an age range of four months to 30 months. Rocephin™ was given; the comparator was high dose amoxicillin/clavulanate for ten days, 80 mg/kg per day. The efficacy parameter was clinical response of week-2 and week-4.

In the French clinical study which had 513 patients, 463 were FDA evaluable, 50 were sponsor not evaluable because of adverse events causing

termination, inappropriate timing of the second visit, non-compliance with medications. Zero were considered medical officer not evaluable.

Trial design issues. High dose augmentin was the comparator -- this is not approved in the United States for this indication. Nasopharyngeal swabs were collected as bacteriologic data. It's not per the IDSA guideline recommendations. There was no blinding. Tympanograms were completed at week-4, not at baseline.

When viewing these results, recall that no changes were made by this medical officer.

So cure rate, week-2, ceftriaxone, 79 percent; augmentin, week-2, 83 percent; and the confidence intervals -- -10.9 to 4.2. Week-4, 59 percent; augmentin, 55 percent; 95 percent confidence intervals; -6.7 to 14.6.

In terms of evaluable population, demographics treatment arms were balanced with respect to age, weight, sex, race, signs and symptoms of otitis medic, tympanogram results and pneumatic otoscopic examinations, with a few minor exceptions.

So here is a side-by-side slide of all the response rates in these three clinical studies. The Roche clinical study, comparator low dose augmentin,

74 percent/82 percent; Klein clinical study, comparator trimethoprim sulfa, 54 percent/60 percent; French clinical study, comparator high dose augmentin, 79 percent/82 percent.

Recall that there were no changes to the French or to the Roche clinical study, and the issues in the Klein study when viewing this data were that 28 patients had recurrent otitis media and they were considered not evaluable in the protocol. And also recall that the second dose patients were included as failures in the standard analysis.

This is a graphical representation of those confidence intervals you've already seen in text. The big bar here is the FDA-recommended cutoffs. The Roche clinical study, ceftriaxone versus augmentin: -14.4 to -.5. Notice it doesn't cross zero. The Klein study, ceftriaxone versus trimethoprim sulfa: -16.4 to 3.6. French clinical study, ceftriaxone versus high dose augmentin: -10.9 to 4.3.

Here are the response rates at the week-4, side-by-side. Roche clinical study versus low dose augmentin: 58 percent success, 67 percent success in the comparator. Klein clinical study: 35 percent success, 45 percent success to trimethoprim sulfa. French clinical study: 59 percent success ceftriaxone

and 55 percent success high dose augmentin.

The confidence intervals for the week-4 subset: -17.5 to -1.2; does not cross zero; Roche clinical ceftriaxone versus augmentin. In the Klein study, ceftriaxone versus trimethoprim sulfa: -19.9 to -.003. The French clinical study, ceftriaxone versus high dose augmentin: -6.7 to 14.6.

At this point we've discussed the clinical studies. We're going to move on to the micro studies. There were two micro studies: one multi-center U.S. study and one single-investigator U.S. study.

The first of these is the Roche bacteriologic study which had 108 patients. It's a prospective, non-comparative, open label study, with an age range of six months to six years. Rocephin™ was given, there was no comparator, and the efficacy parameter was bacterial eradication on week-2 and week-4, study day-14 and 28.

The Roche bacti study had 108 study population: 69 were FDA evaluable; 29 were sponsor not evaluable because of no pathogen or entry violation; ten additional were in the modified ITT because of loss to follow-up or signs and symptoms not consistent with acute otitis media. There were no changes made by this medical officer. There were no

statistical issues.

This is a busy slide but I would like to make sure that you focus your eye to the number analyzed in the summary of the bacti eradication and also to the percent eradicated. This is day-13, this is day-30. Strep pneumo, 38 analyzed; H. flu, 33 analyzed; Moraxella catarrhalis, 15 analyzed -- although 65 percent of pen resistant strains were eradicated only eight isolates were obtained here in the per protocol analysis.

Ninety percent were pen susceptible; 87 percent for beta-lactamase producing H. influenzae; 83 percent for beta-lactamase negative H. influenzae; 79 percent for Moraxella catarrhalis; 100 percent for this one isolate of beta-lactamase negative M. cat.

This slide is a summary of the cure rate for the Roche bacteriologic study, outcome by infection. There were 108 patients. The responses were evaluated on day-13 to 15 and day-30. Week-2, 87 percent success; week-4, 71 percent success.

The second bacti study by Virgil Howie with 203 patients, was prospective, open label, single center study with an age range of six months to three years. Rocephin™ was given but a second injection was given in 33 additional patients at the discretion

of the investigator.

The comparator was CR Bicillin followed by trimethoprim sulfa for ten days; 50 mg/kg of the sulfisoxazole component. The efficacy parameter was bacti eradication at day-2 to 3, week-2 and week-4.

Here you see that the study population is 150 at week-2 because patients were not randomized -- patients who were not randomized who were about 53 patients, were not analyzed at week-2. The FDA evaluable was 125. Ten were sponsor not evaluable because of loss to follow-up and consent withdrawn.

In addition to this ten, 15 more were considered medical officer not evaluable because of recurrent otitis media, otitis media less than 30 days prior. These were the issues with this study. Second dose patients were treated as not evaluable in the per protocol analysis. They were included as failures in the standard analysis.

Patients received a second tap, all but 20 at day-2 to 3. These additional exclusions were added in: recurrent otitis media, otitis media at less than 30 days.

This is a summary of the efficacy results for the per protocol analysis for Howie's study. Ceftriaxone, week-2, 45 percent; comparator, 74

percent; 95 percent confidence interval at week-2; -48.3 to 11.2. Week-4, ceftriaxone cure rate, 34 percent; comparator, 49 percent; 95 percent confidence interval at week-4; -35.2 to 5.1.

At this point I've discussed the clinical studies, I've discussed the peak case study, and I've discussed the bacti study, and I would like to show you a special sub-population analysis. These are the pool cure rates for patients who received two doses of ceftriaxone: 33 patients from Virgil Howie's study and 23 patients from Dr. Klein's study.

The results were, at week-2, 48 percent, and at week-4, 35 percent. There is a paradoxical increase in efficacy. Perhaps it could be explained by viral otitis media.

As no difference was noted between ceftriaxone and controls for morbidity and total adverse events or drug-related adverse events, this will not be the focus of the discussion of safety today. The focus will be on the patients who received two doses of ceftriaxone.

What was significant was diarrhea in those patients that received two doses of ceftriaxone. You see the numbers here. This is two doses, this is one dose of ceftriaxone, this is the comparator of pen

trimethoprim sulfa, and this is trimethoprim sulfa. Thirty-nine percent of patients had diarrhea with two doses of ceftriaxone; 24.5 with one dose; 20 percent with the comparator pen ceftra; and 12 with trimethoprim sulfa.

These were the problematic issues which arose in the review of this drug for otitis media. There was lack of investigator consensus on evaluability criteria, particularly inclusion/exclusion criteria; lack of investigator consensus on endpoints, primary and secondary endpoints.

With this data in mind, I present to you the questions we have for you, our panel. Does the safety and efficacy data presented here support the approval of Rocephin™ for the treatment of pediatric patients with acute otitis media? If no, what additional safety or efficacy data are necessary?

Number two: Are there recommendations that the committee would make regarding the appropriate use of Rocephin™ for the treatment of children with acute otitis media?

And number three: Are there any issues that should be addressed in phase 4 studies?

And certainly not least, I'd like to

acknowledge this long and worthy list of people on this slide and particularly want to acknowledge Funmilayo Ajali and Li Ming Dong for their co-review of this application. Thank you.

CHAIRMAN CRAIG: Thank you, and especially for staying within your time. Questions from the members? Could you go back again when you were talking about the bacteriologic -- when you were talking about the success with the first bacteriologic study? That was presumed eradication, wasn't it, based on clinical data? Or was that --

DR. VIRARAGHAVAN: Presumptive eradication. Only --

CHAIRMAN CRAIG: Right, so we have no documented --

DR. VIRARAGHAVAN: It's not --

CHAIRMAN CRAIG: -- eradication of resistant organisms?

DR. VIRARAGHAVAN: That's correct.

CHAIRMAN CRAIG: Dr. Melish.

DR. VIRARAGHAVAN: Yes, Dr. Melish?

DR. MELISH: How is diarrhea defined?

DR. VIRARAGHAVAN: This was defined per the family members, per the Roche case record form protocol.

CHAIRMAN CRAIG: Was that difference significant?

DR. VIRARAGHAVAN: We did not calculate a significant number; however, what we see is the visual significance of the number here. Yes?

CHAIRMAN CRAIG: I'm sorry. Yes. One of our consultants; go ahead.

DR. GRUNDFAST: In an overview, epidemiologically over long periods of time, how do you assess the possibility that a new indication or a new agent can have a significant, adverse impact on resistant organisms?

DR. VIRARAGHAVAN: That is the discussion that we need to discuss in detail this afternoon. And I think I will leave that answer for the panel this afternoon.

CHAIRMAN CRAIG: Any other questions from the members? If not, we have now, just before lunch, the open public hearing, and I think we have one individual who also has promised to stay shorter than the allotted time so that we can have sufficient time for discussion in the afternoon.

And this is Dr. Jacobs -- Michael Jacobs.

DR. JACOBS: Thank you, Mr. Chairman, committee members, and colleagues. I asked to give

this presentation to give a microbiologic overview seeing I'm a clinical microbiologist, of what I see going on in the field of otitis media.

And I see two things that concern me. I see incredible antibiotic usage with many of the agents do not have wonderful activity against the pathogens we're dealing with -- although some of them are incredibly active -- and I'm concerned about those further resulting in more development of resistance.

And the second point is that I'm very pleased to see in many of the speakers and presentations that the microbiology that clinical microbiologists have been doing and developing MICs and developing most unique science called MIC-ology, actually it has some clinical application. And otitis media is probably one of the best applications we have of this showing that what we're doing in the lab does have some clinical relevance.

And as you can see in this slide -- and this is the same data that's been shown many times yesterday and today -- that annual rates of antimicrobial use for children younger than 15 years of age -- and this is predominantly in the under 5-year age group -- has gone up incredibly between 1980 and 1992, particularly with amoxicillin, but also with

cephalosporins. Trimetho sulfa use is coming down as is erythromycin use, but there's been increased use with newer macrolides not shown on the slide.

And as everyone is very well aware, these are the three pathogens we're dealing with, and as everyone also knows and this data's been shown innumerable times, we're not in the penicillin intermediate era in the '80s and in the '90s; we're now getting into the penicillin resistant era.

But I want to discuss what these terms mean, and also the beta-lactamase positivity rates are now reaching 30 percent, and in some of the presentations you saw 50 percent or even higher in selected populations.

Now, the main point I want to make about susceptibility is, .015 is the baseline susceptibility of pneumococci to penicillin, and these colors are what we call penicillin intermediate and penicillin resistant, but the main point I want to make is that these are terminologies of convenience and not necessarily of clinical significance.

And what I'm prepared to call these organisms is beta-lactam challenged. And the challenge is, can you overcome this degree of resistance with the site of infection and the dose and

route of administration of the drug you're using?

The other point about this slide is that you can take any beta-lactam and with some differences -- but overall the pattern is the same -- your starting point and your ending point are the same. The only difference is these values are different.

In some instances when you have very active beta-lactams the values are the same as penicillin is occasionally a fraction better. When you have very poorly active beta-lactams you'll start off with a value of .5 and end up with a value here of greater than 256. So there's a lot of variability with different beta-lactams.

With macrolides, trimethoprim sulfa, chloramphenicol, there are bimodal populations. We don't run into this problem. These are not erythromycin challenged organisms, these are macrolide resistant organisms, and the current breakpoints we have for macrolides work very well, and for the most part for erythromycin we don't see any strains in this range here. And the breakpoints are recently being refined for macrolides with specific methods, and they work extremely well.

The clinical significance of the beta-lactams though, is a major issue. And just to show

you what the current status is, the National Committee for Clinical Lab Standards -- and for the most part, these are some of the breakpoints that are shown in the product inserts for many of the oral beta-lactams -- are shown as between 4 and 16 micrograms per mil.

And peak serum levels of these agents are typically below these breakpoints with the exception of laracarbef where they're fairly close. And my understanding of these breakpoints are that these were approved for these drugs based on urinary levels of these drugs for treating organisms like e. coli.

And I find it very difficult to see how these get applied to pneumococci and for this reason NC Celius removed these breakpoints in 1995 but they're still there in the product insert, and many authors are very confused about this and use these values for giving definitions, saying that these are the only values available.

However, in 1995, tighter specific breakpoints were approved for amoxicillin, amoxicillin/clavulanate and cefuroxime axetil. And again, you can see these are clinically irrelevant, being several fell below peak serum levels.

The macrolide breakpoints as I mentioned, there's no problem with step pneumo. With Haemophilus

the major mechanism of resistance is beta-lactamase production; altered PBP strains are extremely rare, and methodological differences account for many of these reports as I'll show.

You see values of low levels of resistance, moderate levels of resistance, and high levels of resistance for some of these agents listed, but I have a lot of concern about the rationale for the basis of these determinations. And again, you can see for the most part these breakpoints are on the high side and often above clinically achievable levels of these drugs.

And in addition to that, Haemophilus has another problem; that is of susceptibility testing. In this study, this is what I consider a typical distribution of, or signature of Haemophilus for amoxicillin/clavulanate as it is for many other agents, where MIC_{50} and $_{90}$ are very close to each other. MIC_{50} here at .5 and MIC_{90} is one, and the breakpoint is four.

And you can see here you have a normal distribution and I've shown the 95 and 99.7 percent confidence limits as 2 and 3 standard deviations. And you can see on this group of 2,700 Haemophilus influenzae untypable strains there was zero percent

resistance.

This is another study from the literature of a recent survey of 1539 strains. These are data from the literature; they're not my data. This is an analysis of data in the literature. And here you can see the MIC_{50} was one in contrast to .5 on the previous slide, and here the MIC_{90} which on the previous slide was one, is now eight.

And uncorrected percent resistance is 4.5. If you correct for three standard deviations that falls to 1.2, but again, this is a normal distribution and these strains have not been documented to have any different resistance mechanisms and in some people's hand have not -- this level of resistance has not been reproducible.

But again, you can see if you look at these two studies, one on the basis of the regular parameters of just your breakpoint, this shows 4.5 percent resistance; the previous one shows zero percent resistance. They can't both be right unless these populations are different, and I have no reason to believe or any evidence to believe that these populations are different.

This study included about 700 organisms from the U.S. and they didn't stand out. This study was

entirely U.S. organisms. And I can show you multiple other comparisons showing these distributions with multiple other agents from these different studies, and you get totally different percentages resistance. And the whole issue of the method of testing of Haemophilus needs to be re-evaluated.

In addition, the macrolide breakpoints for Haemophilus also cause a lot of problems unlike strep pneumo. If you look at the macrolide distributions -- and I'm showing the MIC value here in reverse, from .03 up to 32 -- erythromycin has -- they all have unimodal distributions with azithromycin being the most active at .5, erythromycin at 4, and clarithromycin at 4 to 8.

But again, how you interpret these with the unimodal population, no specific resistance mechanism, and for parenteral purposes they all must have the same interpretation. What is seen in the literature as an arbitrary breakpoint is generally taken, and if you look at the breakpoints I showed you on a previous slide, at clarithromycin and azithromycin using four and eight.

With azithromycin that's no problem because MICs generally don't go that high, but for clarithromycin you're calling the population at 16

resistant with no mechanistic mechanism or basis for this.

How this correlates with clinical outcome, again, is one of the positives I wish to bring out -- and again this data has been shown several times. And in a pre-penicillin resistance era or penicillin challenge strains, all of the apparently approved agents for otitis media were active against strep pneumo, and for Dr. Craig's criteria -- this data is from Dr. Craig's analysis.

As we got into the penicillin intermediates challenged group you can see activity of many of these agents fell, with amoxicillin and ceftriaxone remaining the most active. And when you get to penicillin resistance strains, again these two agents remain with all the oral cephalosporins currently available have fallen out pharmacokinetically.

This needs to be combined with the activity against Haemophilus influenzae where the spectrum is different, and also against Moraxella catarrhalis where again, the spectrum is different. But for the most part, a lot of these agents are very close to that 40 to 50 percent cutoff that Dr. Craig has established.

Finally, as you can see here with otitis

media accounting for 40 percent of risk of prescriptions of antibiotic use in pediatrics -- and if this figure is in the 20 to 30 million number range with risk re-infections overall accounting for 75 percent or more of all prescriptions, this is putting incredible selective pressure.

And again, the main message I wanted to get for this presentation is that we need to be concerned about minimizing the selective pressure and also interpreting our susceptibility data correctly by using clinically-appropriate breakpoints. And I hope that someone will take responsibility for developing them.

Thank you for your attention.

CHAIRMAN CRAIG: Thank you Michael. We're back on time and it's time for lunch. But I think to sort of speed things up there were a couple -- I checked with a couple of members and there were a couple of questions they had for the industry presentation, that you might consider over the lunch period and then respond to the committee after that.

The first one is one that I had, and again it's concerned with the pharmacokinetics of the drug. You didn't seem to take into consideration the protein binding of ceftriaxone when you were looking at your

time above MIC. And I think if you take that into consideration -- and again, I don't expect it's going to be 90 percent like it is in serum -- but I expect it would probably still be around 90 percent in fluid.

So that would move your -- 35 is your peak down to only about 3.5. So it's not a bother for me for susceptible organisms, but where I become a little bit more concerned is when one gets up to resistant organisms, which is one of the things that you have, at least in your -- want to have in your claim; that the drug is also active against those organisms.

And so that's one area that I'm concerned about. And then the other one was from Dr. Rodvold.

DR. RODVOLD: One of the questions I had was that you presented data very nicely from Iceland about middle ear fluid concentrations, but as presented you're kind of still coming under the distribution phase versus moving into the elimination phase, and you extrapolated a half-life of 25 hours.

I'm wondering, do you have other information to support that extrapolation, and that is the elimination phase of that middle ear closer to what is in the serum, or is it really up to the 25? I expect, you know, obviously it's hard to retap ears at day-5 to prove those things; I appreciate that problem. But

if you can at least shed some light to us.

Again, like Dr. Craig's concern, I have -- with the protein binding -- with this issue is, I don't think -- and I've done some quick calculations here, it's not a problem with the susceptible pathogens; it's the resistant pathogens of saying that you're staying above the MICs in the middle ear fluid at day-5 and less.

So if you can maybe shed some light on that for us.

CHAIRMAN CRAIG: And I talked with most of them. Anybody else have any specific questions for the sponsor? Okay. We will now adjourn for lunch and we will meet back here precisely at 12:30.

(Whereupon, a brief luncheon recess was taken at 11:30 a.m.)

A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

12:39 p.m.

CHAIRMAN CRAIG: I guess we'd ask first from the sponsor if they had any responses to the questions that were asked before the lunch break?

DR. BLUMER: Thank you, Mr. Chairman. My understanding of the first question was what role protein binding might play in determining the effectiveness of ceftriaxone in middle ear fluid.

And this is a complicated question, obviously. If I could have slide C-5. As you pointed out, it's very clear that -- this is the data from that Howie study in which there were 84 patients who received ceftriaxone and these were all patients who had repeat tympanocentesis done at day-2 to 3. Even though some of these patients went on to have another dose of ceftriaxone, none of them had it before this bacteriologic evaluation was performed.

And you can see as you'd expect, all of the penicillin susceptible strains of pneumococcus as well as all the other organisms, were eradicated from the middle ear. So it's not an issue there.

If I can go back to section 3 now, slide 4. Protein binding of course, is one of the characteristics of ceftriaxone and in adult plasma,

the protein binding is a saturable phenomenon and protein binding is roughly 90 percent.

Now, this is not true for children, to start with, and the protein binding in pediatric patients is somewhat different. Maybe we could have that slide off to show this -- the protein binding for children is somewhat lower, probably related to lower albumen concentrations. But this is data from some infants and young children who have unbalanced ceftriaxone being somewhere in the range of 15 to 20 percent.

So things are a little bit different in children but even with that the question is, how important is this is terms of the activity of the drug? One of the key features of protein binding is that this is -- if we can have the slide back on -- that this is an equilibrium process.

Now, in the middle ear there's normally no protein -- it's normally a space. In the presence of eustachian tube obstruction fluid does accumulate, and in the presence of infection and inflammation, we do get protein that finds its way into the middle ear fluid. The question is, how much?

Normally in interstitial fluid there's approximately ten percent of the serum protein concentration present. So the albumin concentration

in particular, usually runs about ten percent of the serum albumin concentration. However, in the presence of inflammation we'd expect that to be higher; the question is, how much higher?

So I think it's probably useful to take this and look at it in what might be considered an extreme case, and let's assume that it becomes the same as plasma, so that we're going to deal with a situation where we have essentially, albumin concentrations -- because of course, this is a drug that binds to albumin in preference to others here. It doesn't bind to alpha-1 acid glycoprotein or other lipoproteins or gamma globulins in the plasma, it binds to albumin.

Let's assume that the albumin concentration achieves the level in plasma, and let's assume for the sake of this discussion that the binding is about 90 percent. Then I think it's useful to go back to the model and see what that would predict for us.

And if we have an MIC of one for resistant pneumococci, that takes -- I mean, we can fit this to the model very nicely and in fact, we would predict that we would end up with concentrations that would allow us to predict about a 60 percent cure rate -- a 60 to 65 percent cure rate -- which is basically what we're seeing with resistant pneumococcus.

So we go to the next slide please, it probably is easier to look at in terms of middle ear fluid to MIC ratio. So if the middle ear fluid to MIC ratio, looking now at free drug -- if 35 is the peak and we get a level of three -- then we're going to be down here and we would predict 65 to 70 percent cure rate.

The difference between what you'll see with ceftriaxone and what Dr. Giebink showed us with respect to amoxicillin -- which would also do the same thing, by the way, okay. Amoxicillin is also predictably going to -- when you use the higher doses you're going to get a middle ear fluid to MIC ratio that would predict roughly a 60 to 70 percent cure rate.

However, if we can go back one -- the difference if you recall, was that with ceftriaxone we maintain that concentration throughout the entire dosing interval. That concentration stays there. And I know this gets to Dr. Rodvold's question; I'll try and address that in a moment. There's only so many assumptions I can do at one time. I'm assuming my way into a corner here.

(Laughter.)

But if we assume for the moment that we

achieve that concentration, we sustain that for a protracted period of time. I don't have Dr. Giebink's slide, but if you look at that you saw that you maintain that concentration above the MIC in that case only for about an hour-and-a-half to two hours out of the 8-hour dosing interval for amoxicillin. So there's the difference.

But even in what might be considered a worst case scenario, we're sort of already seeing with limited clinical data, what we would predict based on this model, and that's somewhat encouraging.

Now, it strikes me as somewhat unlikely, other examples that we have -- for example, pleural fluid where we do have some data -- it turns out when we look at total versus free concentrations of ceftriaxone in pleural fluid after a single dose, the degree of binding is only about 40 to 50 percent, probably reflecting the difference in protein concentration between plasma and pleural fluid in patients with pleural effusions.

The same is true in work that we have that is not published, looking at cerebrospinal fluids where again, you don't have quite as much albumin but you have lots of other proteins. And you have roughly 40 to 60 percent, in that range, bound.

That would take you -- and if we can go ahead to the next slide, to 5 -- that would take you ahead to move you sort of up on this curve. So if that's the case, it's really going to depend on how much inflammation is there, how much albumin gets there, what the relative equilibrium is, etc.

So I still think that the model holds very nicely and serves to explain what we see. And we would expect to see about 60 to 70 percent based on this worst case scenario, of coverage of the resistant pneumococcus, as long as the MIC doesn't shift much further. If it goes to two we move down a little further and we approximate closer to 60 percent, that sort of thing.

So I think the principles do hold. If I can go to slide 14 from section 3?

CHAIRMAN CRAIG: Before you go on --

DR. BLUMER: I'm sorry.

CHAIRMAN CRAIG: -- can I just sort of ask a question? Those models were based on percent of the dosing interval. What is the dosing interval for a single dose? Is it 24 hours, is it 48 hours, is it 72 hours? What's the dosing interval?

And I think that's the part for the model that we don't know; is what is the aggregate time

above MIC that one needs to be in order to get efficacy? And I think that's why I was asking the question.

You're sure going to be above the MIC I think, even against resistant organisms for 24 hours, but is that enough for a resistant organism or does it need to be out for two or three days in order to do that?

DR. BLUMER: No. Actually -- maybe slide 6. No, I'm sorry, 14 will be fine. Let's try to start there and -- can we go to 15, then? Okay. I think the answer to that is here, all right. And basically, the killing kinetics are determined by time above MIC, so depending on the -- and whether we're twice, three times, four times MIC, you know, based on the particular MIC of the resistant organism --

CHAIRMAN CRAIG: But at eight hours we've still got three logs of organisms left.

DR. BLUMER: We have a 3-log kill.

CHAIRMAN CRAIG: Yes, but we've still got two to three logs of organisms left. It's not sterile yet.

DR. BLUMER: This is obviously, as far as it goes.

CHAIRMAN CRAIG: Yes.

DR. BLUMER: The answer to your question is, beyond this I don't know, but I think it would suggest that this is usually associated with, you know, in someone who has some immune competence this would be associated with eradication and cure. So that we're certainly building on top of immune mechanisms that are already present. That's the best --

CHAIRMAN CRAIG: Yes, Dr. Giebink?

DR. GIEBINK: Scott Giebink. Dr. Blumer, what assay was used to measure ceftriaxone in the Icelandic study? Was that measuring total or free ceftriaxone?

DR. BLUMER: That was measuring total ceftriaxone.

DR. GIEBINK: Total?

DR. BLUMER: Yes.

DR. GIEBINK: And those were children that have chronic otitis media with effusion?

DR. BLUMER: Correct.

DR. GIEBINK: Do you know if they were mostly kids with mucoid effusions?

DR. BLUMER: That I don't know. Do we have an answer to that at all? Whether the kids from Iceland had mostly mucoid effusions? No one knows. If we can go back one slide.

The answer, I think, to Dr. Rodvold's question is -- the answer is, we don't know, and I don't know anyone that has that data. Except to say that what we're dealing with is penetration into a space, and as long as it remains a closed space -- the surface area to volume ratio remains very small -- you would expect a delay in elimination.

So that while you might expect mucosal clearance to mimic plasma clearance because of its vascularity, when you're looking at clearance from a space, this in some ways may even underestimate the duration of presence in that space -- simply because there's just no way to get out.

It's sitting there in the space and you have to rely on Brownian Motion to get it into contract with the mucosa. But there is no data available that I'm aware of that will describe it. So this is simply taking a best guess at that model.

DR. RODVOLD: Can I ask you a couple of questions? Is it possible to get that data like, you know, is it ethical to tap people later on -- which I understand is a problem, but I mean --

DR. BLUMER: What do you think? I think it's problematic. By 48 to 72 hours most of these children are much better, and it becomes a real

difficult ethical question whether you can go in and do another invasive procedure then, to get this additional data.

I have a feeling that, other than in extreme circumstances -- and it may be that over long periods of time after a single dose in patients who come back on day-5 and aren't well or delayed, you might be able to pull enough data together, but not acutely.

DR. RODVOLD: My second question, is there any other space that's like this that there's data in ceftriaxone that reassures the statement, or is there not another space that you feel is equivalent to this?

DR. BLUMER: Well, I think the other body cavities -- you know, in cases where people have looked at, for example, time-dependent clearance from pleural effusions, time-dependent clearance from cerebrospinal fluid -- there is a discrepancy, there's a prolonged half-life in those. But all of those data suffer from the same problems: relatively short sampling time.

No one that I know has done the sort of analysis where you try and strip out what might be considered the absorption phase from -- there just isn't enough data to do that. So we're really stuck with what's ethical.

I suppose one could go ahead and try and model this in animals but I'm not aware that it's been done yet. And even then, you raise questions. So I think we're stuck but as I said, one would expect that in a closed space like this -- now, if the eustachian tube suddenly opens up and drains, obviously, the concentration is going to fall. So some of these things are going to be patient-specific.

CHAIRMAN CRAIG: Okay, thank you, Jeff. What I have put up on the screen there are the questions that were asked by the FDA to the committee. And I think what I'd like to start with, have some of our consultants sort of looked at the first question which is: Does the safety and efficacy data presented support the approval of Rocephin™ for the treatment of pediatric patients with acute otitis media?

And I guess I might just give sort of my review of sort of what I thought they were telling us from the data that we heard this morning. Is that the drug appears to have excellent bactericidal activity against the various pathogens that are associated with otitis media using the 2-tap method for bacteriologic cure.

However, when it was looked at in the comparative studies, it looked like it was just a

little bit less effective than low dose augmentin, but equally effective to high dose augmentin -- which again, I have a little trouble understanding that -- and that it also looked to be equally effective with TMP-sulfa.

From the FDA's point of view, is that sort of what I was seeing from the data?

DR. VIRARAGHAVAN: That is correct, but I would like to just comment on the second tap patients in Howie's study. Can you please put up the bacteriologic eradication rates of day-2 to 3; it's slide number 71.

This data was provided by the sponsor, and what you need to see here are those 33 patients in this study that have two doses of ceftriaxone, and this is the results from that in terms of eradication. And eight of the 33 were not analyzed; 17 of the 33 had eradication; two of the 33 were new infections; one of the 33 was persistent; and five of the 33 were presumptive eradication.

I just wanted to show that information to you.

CHAIRMAN CRAIG: I thought the numbers, at least my look at the numbers before, is I thought the eradication rates were higher, but that -- are these

presumed eradication rates based on clinical data?

DR. SOLSKY: I can respond for a minute about this. In regards to the Howie study, of the 33 patients who received a second dose, if you recall this was the second -- it was a double tap study -- I'm sorry.

In regards to the Howie study, 33 patients received a second dose and if you recall the study design, patients were tapped the second time at day-2 to 3 prior to receiving the second dose. And 32 of the 33 patients who were tapped a second time had total eradication of their baseline pathogens. The one that remained was, if you recall from one of the other slides, was a new infection. There was no persistence of baseline pathogens in Dr. Howie's study.

CHAIRMAN CRAIG: Now, are your results based on presumed eradication based on clinical data?

DR. VIRARAGHAVAN: These results were based on what the sponsor provided to us, and only 17 of the 33 had eradication. Presumptive eradication was five of the 33; persistence was one of the 33. Two of the 33 had new infections; new infection as defined as the pathogen isolated in the follow-up but not presented baseline -- persistence of pathogens cultured at

baseline is still present in the day-2 to 3 culture.

CHAIRMAN CRAIG: So all these percentages add up, is that --

DR. VIRARAGHAVAN: This adds up to 33.

CHAIRMAN CRAIG: Okay. So that you're not saying that a new infection -- only 30 percent of them were eradicated?

DR. VIRARAGHAVAN: No, I'm not saying that.

CHAIRMAN CRAIG: Okay. You're just saying how the eradications were distributed among --

DR. VIRARAGHAVAN: I'm telling you the breakdown of the numbers.

CHAIRMAN CRAIG: Yes. Okay. Thank you. So, again getting back, there seems to be some equivalence with TMP-sulfa, also with high dose amoxicillin from the European study, but not quite from the U.S. study; it tended to be just below, but .5 didn't cross zero.

So with that sort of data the question that the committee has to address is: Does the safety and efficacy data presented support the approval of Rocephin™ for the treatment of pediatric patients?

And I would like to look at it first -- two ways. I would like to look at it just with penicillin susceptible organisms, and your usual Haemophilus and

Moraxella, and then take the question of resistant pneumococci which is another statement which was in the request from the company separately.

So Scott, would you like to comment?

DR. GIEBINK: I do think that the question here is pneumococcal disease, and I think it's good to focus on the pneumococcuses you phrased the question, Bill. I'm much less worried about Haemophilus otitis and considerably less worried Moraxella otitis, simply because spontaneous resolution rates are greater, although there is some concern that perhaps the Moraxella catarrhalis organism is changing over time and I don't think we know for sure that its virulence characteristics are going to be as benign as they are now in the future.

So all of that aside and focusing on the pneumococcus, I believe that the data are sufficient to show both bacteriologic and clinical efficacy of single dose Rocephin™ for the penicillin susceptible organisms.

And probably what we are arbitrarily -- or NCCLS has arbitrarily defined as penicillin intermediate; the healthy side of the challenged pneumococci that Dr. Jacobs was talking about -- I'm a little bit concerned about the penicillin resistant

pneumococci. Granted, the small numbers that we have in the bacteriologic study suggest that it will be active, but the clinical data worry me.

There are issues around the clinical assessment of those patients that fail the clinical outcomes, all of which have been discussed here this morning. I think that if single dose ceftriaxone were to be approved broadly for pneumococcal disease it would have to be linked to a re-review on the penicillin resistant issue and additional studies directed at those patient.

Bear in mind that all of the large, clinical trial data that we've seen were performed before we really had the invasion of penicillin resistant pneumococci on the scene. So I'm very cautious -- not necessarily skeptical, but cautious -- about the penicillin resistant indication.

CHAIRMAN CRAIG: Thank you. Dr. Wald?

DR. WALD: Yes. I think that there are a couple of issues here, and the first one is the one that we're talking about and that is, will ceftriaxone work for acute otitis media?

And I would agree with what has already been said; that certainly for susceptible organisms it's clear that we can get eradication and probably cure in

some significant proportion of patients, and what remains to be determined there is the precise efficacy in resistant organisms.

But I think there's a second, much more global issue that we have to ask ourselves about and that is, what will be the consequences of approving this drug to be used in acute otitis media and recommending its use in that instance? And while I'm certainly someone who believes that acute otitis media needs to be treated with antibiotics, let's think about which children are likely to receive this.

I mean, we talked today about issues when there might be difficulties with compliance; we talked about children who might now like the taste of drugs and who might be difficult to medicate. And I think it's easy to imagine that one could get wholesale use of ceftriaxone in impoverished children, many of them very young, for whom in fact, short course therapy may not be optimum.

I think ceftriaxone is an incredibly potent drug and I don't really want to lose it for use in serious infections. We've been participating in a multi-centered, pneumococcal surveillance study since 1988, and I just called Ed Mason during the lunch break just to find out the most recent data.

In 1995 through 1996, on the basis of more than 600 isolates -- systemic isolates and middle ear isolates -- the resistance to ceftriaxone was 16 percent. So far in 1997, on the basis of 190 isolates, again mixed, ceftriaxone resistance is 23 percent. Roughly half of it is high level resistance.

So while people have tried to assure us today that the kinetics of this drug are not going to aid in the emergence of resistance, we are living and seeing emerging resistance. And I think that we can anticipate wholesale and inappropriate use of what is a very valuable drug, inappropriately.

CHAIRMAN CRAIG: The question I would have is, how much of that is just due to antibiotic use in general as compared to a specific compound?

DR. WALD: Well you know, no one knows the answer to that.

CHAIRMAN CRAIG: Well, I guess I'll ask Scott Dowell, there are some studies I think that have been done in France -- maybe the CDC is involved in some of these -- of trying to look at what are some of the risk factors for developing penicillin resistant pneumococci.

We heard from the sponsor that in Italy they tend to use parenteral cephalosporins and the

incidence tends to be low as compared to places which use a lot of oral drugs. Is there any other data that you're aware of, anything from the CDC, that might shed some light on that question?

DR. DOWELL: Not really. As you point out, there are a couple of small trials that have attempted to look at different dosing regimens and tried to look at the effect of different dosing regimens in terms of duration, total dose, level of the dosing, and sorting out whether those different regimens are more or less likely to induce resistance as measured by follow-up nasal swab surveys.

And we saw some data today about nasal swab surveys which I think are provocative but not convincing, and I think that similarly, to me the data from Italy are maybe not even provocative.

We can look at our surveillance system, for example, in the United States and say that the rates of penicillin resistant pneumococci in Oregon are less than ten percent, in Atlanta they're more than 30 percent. And does that mean that that's because we're using more or less injectable drugs in Atlanta versus Oregon? No, I don't think so.

And so I think the observed differences between practice in Italy and neighboring France and

Germany are just anecdotes and not a whole lot more than that. I think the question about whether widespread use of injectable cephalosporins in doses like this will be less likely to lead to pneumococcal resistance is a good one for further exploration.

CHAIRMAN CRAIG: I think the only study I'm aware of is the one that was presented at ICAAC maybe two years ago -- or, I think it was two years ago from the French -- where they had been following in a close space so that they could follow the development of resistant organisms.

And what they tended to find for risk factors -- I think the main two was -- marginal therapy -- in other words, low doses of the drug, and especially for long periods of time. And I think in that, one of the reasons why prophylaxis has sort of gone into disrepute just because of its potential to lead to more colonization and leading to more resistant organisms.

DR. DOWELL: I've seen that study by, I think it was Claude Carbonne and his group --

CHAIRMAN CRAIG: Yes, right.

DR. DOWELL: -- in just abstract form, too --

CHAIRMAN CRAIG: Yes, that's all I've seen

it, too.

DR. DOWELL: -- and I agree, I think it's provocative just like the data we've seen this morning. It's an area for further study. But I have to say that I think from what we know, I don't think that -- I think it's hard to be convinced that ceftriaxone is going to be immune, either to MIC creep or immune somehow, to inducing resistance or immune to seeing pneumococcal resistance emerge at higher and higher levels down the line.

We saw data yesterday from the CDC Sentinel Surveillance System which was shut down in the late 1980s because we believed, and the experts told us, that pneumococci were not going to become resistant to penicillin. And obviously that was a mistake, and that was an expert opinion at the time. And so I think expert opinion only gets you so far.

CHAIRMAN CRAIG: Dr. Giebink.

DR. GIEBINK: Well, not being an expert --

(Laughter.)

-- I just wanted to point out for the committee the study, what's been going on the last several years in Reykjavik, Iceland, that has demonstrated a very clear relationship between oral antibiotic use and emergence and then subsequent

decline of the single clone of 6-B pneumococcus that emerged as oral antibiotic use was increasing and documented very clearly by the Public Health Department.

And then as there was governmental action taken to reduce oral antibiotic use, the incidence of this clone, which is the only one there, decreased proportionately. So it's very clear -- it's the only evidence I've seen in the world that shows in a semi-closed population, this 1:1 relationship between oral antibiotic use and emergence of a resistant pneumococcus.

CHAIRMAN CRAIG: Do our other consultants have any comments? Dr. Reller, you look like you have something to say.

DR. RELLER: As I read through the data and listened to the presentations this morning, one of the most striking things to me is, I was surprised in the clinical trials that this drug did not perform better than it did.

How might it be used? If it's used initially, broadly, there are some potential costs with that as Dr. Wald presented. If it's used more selectively as one might think about because of the certainty of compliance -- for example, one might use

it where other oral agents had failed or there was recurrent disease -- and based on the concerns raised and the relative paucity of data on the intermediate and frankly, fully flagrantly resistant pneumococci, might be the very place where you would expect even less success than the marginal efficacy that we've seen for those organisms.

Maybe this is due to the protein binding. So that one of the issues might be for penicillin resistant pneumococci that more than a single dose would be appropriate or necessary. So that I think we need a lot more data for resistant pneumococci, and I'm uncertain about exactly what would be the best way to use this drug that is certainly safe and is efficacious, but not as much as I would have thought based on the pharmacodynamics, pharmacokinetics.

CHAIRMAN CRAIG: Ron Dagan reported at this year's ICAAC, some data specifically in patients that had failed therapy using the drug. I think it was three doses if I remember, was what he used in that study. And they had a significant number of his intermediate strains and the drug did very well.

And I agree with you. I'm a little concerned with just one dose for those more resistant organisms, and clearly would like to have more

information to convince me that it doesn't need more doses or possibly, a higher dose. I think when you start giving more doses that makes it not as convenient as being able to give it as a single dose.

Yes, Dr. Azimi.

DR. AZIMI: What about a higher dose? Does the sponsor have any data on perhaps, one single dose of more than 50 per kilo, and what would be some of the pharmacokinetic studies of that? I don't know if that's available at all.

DR. SOLSKY: No, there is no other information on that. We only studied, in all our clinical trials, a 50 mg/kg up to a maximum of one gram.

CHAIRMAN CRAIG: Yes, Dr. Parsonnet.

DR. PARSONNET: I sort of wish I'd asked this question before but, in the clinical studies and the comparator arms, what was the compliance like in the comparator arms and how did that impact the efficacy of the drug?

DR. SOLSKY: The compliance actually, in all of our clinical trials, was very high for the oral comparator, and one could say almost that in regular clinical practice, that it's artificial, because we were seeing rates as high as over 90 percent

compliance. And that's sort of based on, obviously, the controlled clinical trial. It's an artificial situation.

CHAIRMAN CRAIG: And I guess the only other question that some of us had also, that we were tossing around at lunch was -- and Dr. Klein probably, might be able to answer or you probably, too -- was in his study where the people got the second dose, was that written in as an option right from the very beginning, or was that something that the physicians did because the patient wasn't doing as well?

DR. KLEIN: No, that was one of those embarrassing things that comes to fore in a forum like this, in the sense there was an ambiguity in the protocol that some of the participating physicians interpreted as permitting a second dose.

And when we reviewed our first couple of dozen cases, we noted that they were using it without specific criteria. And so we reviewed the protocol with them and that ended. But there were no second dose cases after the first couple of months of the study.

So it was not -- those cases which have been included in the intent-to-treat analysis were excluded in our published report.

CHAIRMAN CRAIG: Okay, thank you. Yes, Dr. Francis.

DR. FRANCIS: Just a quick comment on the adherence and compliance, and I suspect that's sort of an underestimated phenomenon that we need to discuss a little bit more. We know from general population studies of complex regimens the average adherence being -- taking the drug when you're supposed to, is about 40 percent.

It turns out that compliance and adherence are not dependent on indigency, education, where you live. And I was wondering in this case, where we're looking at ceftriaxone compared to other drugs at their most optimal use, truly reflects clinical situations.

As a clinician I'd be more inclined to use the injection only because we know that at least 60 percent of the population will not take it in the proper way, and having explored the incidents and problems of resistant diseases because of that, that's an issue that I think that we need to discuss in a number of different infectious diseases.

CHAIRMAN CRAIG: Okay. Any other comments or -- yes?

DR. GRUNDFAST: One of the most dreaded

complications of otitis media is meningitis and currently, I think that ceftriaxone is one of the agents used for the treatment of meningitis in young children.

I'm wondering if anybody on the panel or anybody else present has information of historical nature or from an analogous situation to let me know the potential impact of the use of ceftriaxone for the indications proposed today on the future treatment of meningitis in children? And that would be a subset of those children who have acute otitis media.

DR. AZIMI: You know, in pediatrics ceftriaxone is being used more and more in the emergency room for febrile children who are presumed to have sepsis, and the use is really almost out of control; it's being used all the time. Anyone who's hospitalized has had a charge or two of ceftriaxone. So I don't know that this indication is going to make any difference in that already established practice.

DR. WALD: I would just say, we looked at -- 40 percent of the prescriptions are written for otitis media, so while you're right, there's a tremendous amount of abuse of ceftriaxone right now in ERs, now it will be in every practitioner's office.

I mean, we heard the panelists say -- or

someone from the FDA -- that as a practitioner you're concerned about compliance. This is the solution. And I think that it could so easily happen that there would be rampant abuse. You know, I want this drug for selected cases of acute otitis media, and I can use it right now for selected cases, but I'd think twice about it. That's different from advertising it.

Let me just say a word about the numbers that I quoted for resistance. Roughly the systemic isolates that are resistant -- S. pneumoniae that are resistant to penicillin in ceftriaxone that are recovered from the system -- either the CSF or the blood -- are about one-half the rate of resistance as those that are found in the nasopharynx in middle ear.

So I think by creating 23 percent ceftriaxone resistance in children in daycare -- because we're talking about children under two years of age -- that we really are creating a situation in which we're going to favor this organism.

CHAIRMAN CRAIG: Well again, I guess I would come to -- I think the question is, the child is probably going to get treated, and in terms of resistance the question is: is ten days of an oral agent more likely to lead to selection of a resistant organism than one shot of a parenteral drug?

And while we don't have a lot of data to answer that question, I personally would believe that it would be more likely to occur with a longer course of therapy than it would with a shorter course of therapy. But that's as I say, my impression.

Scott, go ahead.

DR. DOWELL: Yes, I agree with you, and I think you could ask the question in a different way, too. Given that there are 24 million courses of antibiotics for otitis media each year, those are going to happen whether they're given with amoxicillin or another oral cephalosporin, or whether they're given with intramuscular ceftriaxone.

So really the question becomes, if you want to be sure that ceftriaxone still works for meningitis, is giving ceftriaxone rather than cefpodoxime or amoxicillin more likely to drive pneumococcal resistance?

And I think there are theoretical reasons that -- someone else may want to speak to this -- that first of all, treatment with many of these agents can select for resistance to many of the other agents. In fact, a study in Iceland showed that the biggest risk factor for penicillin resistant pneumococci was high doses of trimethoprim sulfa which doesn't appear to

make any sense on the surface of it.

So that you don't need to treat with ceftriaxone to select ceftriaxone resistance probably. And yet the next question is whether treatment with different antimicrobials, if you switch from most kids getting amoxicillin to a highly theoretical situation where many kids are getting ceftriaxone, is not going to drive resistance any quicker.

I think there is some evidence that changing the penicillin binding proteins can happen with a single step change for cephalosporin, whereas it takes multiple steps for the penicillins. I see some people nodding. And so I think that, in my mind the theoretical concern is that if you switch from treating most kids with otitis media with penicillin to most kids with ceftriaxone in general, that that theoretically could be of a concern.

I don't know of evidence that treating with ceftriaxone is more likely to induce ceftriaxone resistance than treating with cefaclor or cefpodoxime is. I don't know if anybody else knows about that.

CHAIRMAN CRAIG: Scott -- Dr. Giebink.

DR. GIEBINK: I share Scott Dowell's comments because the major compounder -- certainly in Pittsburgh and elsewhere in the country -- with the

widespread use of ceftriaxone for the febrile infant, has been heavy marketing pressure of these other oral cephalosporins, notably two of them -- cefixime and ceftabuten -- that barely exceed MIC and are probably being dosed and achieving sub-MIC concentrations which are exactly the pharmacologic conditions that induce resistance in one-step cephalosporins.

So I would not find any comfort at all in reserving ceftriaxone for acute otitis media on grounds that you're going to protect pneumococci from developing cephalosporin resistance, because I think the greater good would be achieved by limiting the use of some of these other oral cephalosporins.

CHAIRMAN CRAIG: Just one -- Dr. Applebaum, one quick comment.

DR. APPLEBAUM: Yes, can I just make a few comments here, please?

CHAIRMAN CRAIG: Very quickly.

DR. APPLEBAUM: Okay, three minutes.

CHAIRMAN CRAIG: I'm not even sure it's going to be three minutes.

DR. APPLEBAUM: Okay. I'd just like to -- I've got some slides here -- there's obviously not enough time --

CHAIRMAN CRAIG: No.

DR. APPLEBAUM: -- but I'd just like to take issue a little bit about the fact about the data from Italy because here you've got a country in the Mediterranean surrounded by all the other Mediterranean countries which are absolutely swarming with penicillin resistant pneumococcus. And the only common denominator that we can think of is, it's the only country where they use intramuscular, large intramuscular antibiotics and very little oral.

Parenthetically, we've got another corollary to that in Asia -- Michael Jacobs and I are doing an Asian pneumococcal surveillance study. And we've got the same situation in India compared to Korea and Japan. To our great amazement, in India the incidence of DRSP -- and this was done properly in various centers recognizing the country is very big -- and the incidence of DRSP is less than five percent.

Again, almost no oral cephalosporins, whereas in Korea where it's 80 percent and Japan where it's about 50 percent plus, a large use of oral cephalosporins. And especially in view of the fact of the pharmacokinetics which you saw earlier this morning, of the oral cephalosporins compared with ceftriaxone. I would submit that they are probably more the culprits for the development of DRSP.

CHAIRMAN CRAIG: Thank you, Peter. Yes?

DR. PARSONNET: Just aside from the resistance concerns which I think are very serious, I have a few other concerns and that is, that I think the studies show that it doesn't look as good as the comparator drugs.

I think the best study that was pointed out as being the best study, it was significantly worse than the comparator drug, and in two other of the studies which were smaller and had some flaws, it also just didn't look quite as good as the comparators that we're talking about.

And I suppose that's true about -- that my feelings about that are tempered a little bit because the compliance was so that that may not really reflect what happens in real life. But we don't really know what's going to happen in comparison to these two drugs in real life.

And the second issue is that this will be the drug of choice if it is licensed for this practice, and not just because physicians will chose it because it's easy, but because it will be advertised to parents, and we've seen that parents like this drug.

We're showing data from the company that

parents like this drug. So the question is, do we really want a drug without the resistance concerns, that looks like it may not be as good and will be the treatment of choice just because of the ease of administration?

CHAIRMAN CRAIG: I guess getting back to -- not as good -- the problem I had with looking at the data was that it wasn't as good as low dose augmentin, but it was as good as high dose augmentin; which I have a little trouble understanding why it should be good as even a higher dose of agumentin but if you use a lower dose it's not as good.

DR. PARSONNET: All I can say is, from the presentation and from my reading of the data, in one study that was really very well done, it was worse than the comparator drug.

CHAIRMAN CRAIG: Yes. Go ahead, Dr. Danner.

DR. DANNER: I wanted to ask Dr. Wald -- you said that you actually wanted to use this drug for selected patients with otitis media as opposed to having a general indication for anyone with otitis media. What is the group that you would use the drug in?

DR. WALD: If I had a highly resistance pneumococcus. We do a lot of tympanocentesis in

Pittsburgh. If I knew that I had an organism that was resistant to clindamycin, and resistant to penicillin, and susceptible to ceftriaxone, you know, it would be a very attractive drug to use. Because my alternative would be to admit the child to hospital and treat with parenteral erythromycin.

So I think this is a tremendously, biologically potent drug. I think I'd like to have it for serious systemic infections, and I would use it for selected cases of otitis media. If a child was vomiting one would consider -- I mean, there are indications for its use. I don't think it's a preposterous thought; what I'm really concerned about is abuse.

DR. DANNER: But using it for resistant pneumococcus or intermediate resistant is probably the place where we don't have good and efficacy.

DR. WALD: Yes, but I have susceptibilities I'm talking about -- I'm holding in my hands. I know that the organism is susceptible to ceftriaxone. I had just this situation yesterday.

DR. HENRY: Would you use it at 50 or 100 mg per kilo?

DR. WALD: Well, I guess I would have thought of using it at 50, and I also might consider

giving a second dose. You know, I'm not sure that I would regard that as complete treatment, but the point is it would permit the use of outpatient therapy and daily observations in such a child.

CHAIRMAN CRAIG: Dr. Henry, did you have any other comments?

DR. HENRY: No, I just wanted to know about dosing.

CHAIRMAN CRAIG: Anybody else have any comments? Because I think we need to -- we're getting close to where we need to take a vote. Yes, Dr. Giebink?

DR. GIEBINK: Just one more thought. The age subject that Dr. Wald mentioned. Remember, the age analysis in the Hoberman study that I showed you at the end of my presentation, that children under two years of age and marginally for the 2- to 5-year children, given five days versus ten days of agumentin treatment did not fare as well -- the shorter course treatment.

So that if in fact, we're getting a shorter course of ceftriaxone combined with the issues around pneumococcal resistance we've talked about, it may be that that younger population is a group that you could carve out as a population that would need additional

study before the drug would be approved in that age group.

That would also have the side benefit, if you will, of eliminating the drug from routine use in the daycare population.

CHAIRMAN CRAIG: I guess I'd ask the FDA, is in their analysis of the data that was there, was there any age group differences?

DR. VIRARAGHAVAN: We did not do that analysis, Dr. Craig.

DR. SOLSKY: The sponsor has.

CHAIRMAN CRAIG: The sponsor has, okay.

DR. SOLSKY: E-44. On this chart -- this again, is an intent-to-treat analysis that we're showing here. And this breaks it down for each of the comparators, compared to ceftriaxone in terms of breakdown -- if less than 18 months; 18 to 36 months; and greater than 36 months -- for each of the four U.S. studies as well as the French amoxicillin/clav study.

One sees that there is a trend towards a greater increase in cure rate with increasing agents greater than 36 months. However, there are obviously, substantial cure rates at less than 18 months as well. And as you can see also, it is comparable to the

comparatives in the situation.

CHAIRMAN CRAIG: Okay, thank you. Dr. Grundfast.

DR. GRUNDFAST: Sorry, just a very quick question. In a study on outcomes for management of otitis media being initiated by the Academy of Otolaryngology, Head and Neck Surgery, we actually have built in to the study a measure of the child's preference. And even though the children may be young and non-verbal, we have picture scales to determine some of their preferences and outcomes for management.

I know the children were young in the study, but what you showed was the preference of the parents for a parenteral administration of an antibiotic. Was there any consideration given to the preference of the children? And it's not impossible to do that. But was any consideration given?

DR. KLEIN: I can only speak -- no, there was no analysis. My personal experience based on otitis in three children, is that a couple of those children would hide in the closet and when offered the alternative of hiding 30 times during a 10-day period, might choose a single dose and it's over.

CHAIRMAN CRAIG: Thank you. Okay, what I want to do is take the first question, but what I'd

like to do is take and not have us consider resistant organisms and just look at it from a point of view of taking out the resistant pneumococci but leaving everything else in.

All those that feel safety and efficacy data does support approval of Rocephin™ for the treatment of pediatric patients with acute otitis media, raise their hands.

Those opposed? Any abstentions? One abstention. Okay.

The next question is, I'd like to ask the same thing but now I'd like to add in resistant pneumococci. So all those that believe that the data allows the inclusion of resistant pneumococci, raise their hands.

I see nobody. Any abstentions on that second? No. So I assume everybody is voting "no".

Okay, the next question is number 2. Are there recommendations that the committee would make regarding the appropriate use of Rocephin™ for the treatment of children with acute otitis media? Yes, Dr. Danner.

DR. DANNER: What I've heard is a concern that this will become -- you know, go into very, very widespread use and maybe somewhat inappropriately, and

that that may then drive resistance and make a very good drug for a serious infections in the hospital less useful.

So given that, it seems to me that it might be reasonable to in fact, suggest specific situations where one would consider using this drug as in a child with nausea and vomiting who cannot tolerate or take the PO drug, or situations where it's felt that compliance is going to be a tremendous issue.

And maybe try to limit, or at least suggest to the community, that the drug be used in a limited way and not just driven by parent preference, and perhaps the preference of practitioners who I guess, might be able to charge for the administration of the parenteral drug and therefore there might be other motivations for using it.

CHAIRMAN CRAIG: Yes?

DR. BANKS-BRIGHT: As I listen with respect to the second question, the issue of ease of dosing and so forth, and which patients to recommend Rocephin™, as an adult infectious disease specialist I'm remembering the days of the use of vancomycin on adult patients, and particularly in renal dialysis patients and so forth, where physicians -- as IV physicians and many other physicians -- we came up

with all kinds of reasons why vancomycin should be used, particularly when the patient had an enterococcus or staph epi or staph aureus.

We came up with every reason in the world why that patient had to have vancomycin as opposed to, you know, first generation cephalosporin and so forth. And I see the problem that we have come to now when we're doing everything that we can not to prescribe vancomycin.

So I guess -- and I have to admit that as a parent and having been through this otitis media thing now for about 20 years, that not one of my children ever completed a 10-day course of antibiotic therapy. And I would certainly be one of the parents in favor of that from an emotional standpoint.

But as an infectious disease specialist I know when you start making criteria about who should be included, physicians will come up with every single reason why that person should be included as opposed to being excluded.

CHAIRMAN CRAIG: Any -- Dr. Rodvold.

DR. RODVOLD: I think some of the data that was presented at the end and if there's others that wasn't there -- particularly the age factor that came up as a question and then the sponsor showed data --

I'm not sure how many people realize that. And anything that can be done to help point that out.

I know it was comparable to the comparator drug but you know, maybe that -- the more educational-type things for the practitioner that would help them as well as the issues that we're talking about, I think has to be done maybe in concert.

The sponsor can help provide the agency that they're going to do that for the good of mankind, the good for their drug,and good for health sciences. I encourage that some of that can be worked out and supported by both groups.

CHAIRMAN CRAIG: Yes, Dr. Banks-Bright.

DR. BANKS-BRIGHT: I just have one other question about the adverse effect of -- and that still sort of bothering me -- the issue of diarrhea and I think it was 24 percent or 25 percent --

CHAIRMAN CRAIG: That was with two doses, I think.

DR. BANKS-BRIGHT: With two doses --

CHAIRMAN CRAIG: Or, 38 percent with two.

DR. VIRARAGHAVAN: Thirty-nine.

DR. BANKS-BRIGHT: And I guess I still haven't had an answer to, how was diarrhea defined? I mean, Dr. Melish asked that but I'm not sure that it

was -- I mean, one loose stool does not make diarrhea. So I guess --

CHAIRMAN CRAIG: Dr. Klein?

DR. KLEIN: As one of the investigators I can tell you, it was defined in the eyes of the beholder. So that --

(Laughter.)

-- if a parent said that there was an alteration in the stools, they thought it was diarrhea, it was diarrhea.

DR. BANKS-BRIGHT: So what --

DR. KLEIN: But it was -- you had comparable drugs. So that, for instance in the augmentin study, the diarrhea proportion was higher. But there was no fixed definition.

CHAIRMAN CRAIG: Yes, Dr. Henry?

DR. HENRY: I guess this applies to question number 2 about the recommendations we would have about the appropriate use. If the recommendation that the pharmaceutical company is proposing is that the proposed dosage would be for the treatment of acute bacterial otitis, a single IM injection of 50 mg/kg, will that really work in kids under 18 months or under two years of age?

And if it doesn't and yet one single dose

has become standard of care and HMOs and other insurance companies latch onto that, does that mean that the second dose won't be covered? I mean, so I think how it's worded may have to be looked at very closely.

CHAIRMAN CRAIG: Okay. Are there any -- I've heard some recommendations for age. Is there anything that's sort of universal among the committee that they would like to propose? Dr. Melish, anything that you --

DR. MELISH: Well, I'm not sure that the data's strong enough to say it shouldn't be used in children under a certain age. And in thinking about it, I probably share the disappointment that other people do that this drug wasn't more efficacious. But it may be that that's where we are at this time in the United States; that we can't count on a drug that with one course is going to be very efficacious.

I think it's very important then, how it's marketed. It certainly shouldn't be said that this is better than anything because it's not better than anything. Maybe if they do studies with pharmacodynamics with higher doses, we can find something that's better. But this isn't better.

But I don't see that we can strongly -- if

we're going to say it's okay for otitis media ordinary cases, I don't know how we can really give too much guidance.

CHAIRMAN CRAIG: I guess, at least what I've tended to see the FDA put in the packet insert, is exactly what the data shows, which would probably mean that they would say, in one study it didn't quite reach equivalency, while you know, the other two studies did -- at least that's what I would think you'd probably do.

DR. CHIKAMI: Within package labeling there is often a description of the clinical trials which support the indication. And Dr. Craig, you're right. We describe the basis for -- or the data that were presented in the NDA. And that description, both in terms of how the indication is written and how the clinical studies are described, form the basis for the product promotional materials.

CHAIRMAN CRAIG: Dr. Blumer.

DR. BLUMER: As another one of the investigators, I think one of the things I'm hearing which is, is a difference between our clinical assessments of patients and the kind of data analysis that the FDA required. I, as an investigator, was quite surprised at the data analysis that was fed back

and the end of the study because it didn't really reflect clinically what we saw.

Anyone who wasn't a complete cure at the end of the study -- that means essentially, their tympanic membranes looked normal except for having effusion -- was counted as a failure.

Now, of the failures, very few of these children required additional treatment with drugs -- and this is in either arm of the study. So I think that the data for statistical analysis represents what we would call effective therapy. And I think we need to keep that in mind as you're thinking about the answers to this second thing. Because it just doesn't really reflect how we practice medicine.

CHAIRMAN CRAIG: I guess I'd ask Scott and also Jerry, obviously, with this -- it's only been since the FDA clinical trials that one's had a lot more of the follow-up of the ear. Is that been doing repeat exams or is that something that's been with clinical trials right along?

DR. KLEIN: I'm not sure of your question.

CHAIRMAN CRAIG: Well, doing physical -- I mean, looking at the ear with otoscopy.

DR. KLEIN: Oh, no, that's pretty standard for the past 30 years. But I do want to point out

that I noticed -- and I wanted to congratulate the members of the FDA who went to the trouble of looking through over 2,000 records and reconsidering each one -- but the IDSA FDA guidelines spelled out in the Clinical Infectious Disease issue in 1992, were not followed completely.

So at some point the FDA chose a number of areas where they excluded patients, such as those with recurrent otitis media, those who had an episode of otitis media in the prior 30 days. The IDSA guideline says no episodes within seven days.

A couple of other areas where I thought the rules were being made up or had been revised. Subsequent to the publication of the IDSA guidelines -- now, there may be reasons for that and we can hear about it -- but these were studies done in 1990 to 1994. The publication of the guidelines was 1992. I think it established the standards of practice for investigators as of those time. And those are the criteria that you've heard today.

CHAIRMAN CRAIG: Where there any changes in the points to consider?

DR. SORETH: Back in March of this year we presented, at a public meeting with this advisory panel, the evaluability criteria which included acute

otitis media. It was an effort undertaken by the FDA to finally put down in black-and-white, what were the evaluability criteria that we were using in any given infectious disease indication.

And although we did sponsor via contract, the IDSA guidelines, we do not have necessarily, 100 percent agreement with the specifics of each and every guideline for each and every infection. So we discussed in March then, the evaluability criteria for otitis media that we by-and-large had been applying to sponsor's applications but had never formally put down in writing.

That included excluding cases of recurrent otitis media in acute otitis media trials because the entities are not identical, and it also included excluding patients who had another antimicrobial for acute otitis media -- I believe within a 30-day period as opposed to a 7-day period.

So it's not that we're making the rules up as go along every day, but actually we tried to codify and put down in black-and-white what we had been applying across the board to sponsor's applications. That's the first point.

The second point is that the trials that we've seen today, with the exception of the multi-

centered bacti trial, were comparative trials, and even though we talk about having what is a very conservative analysis of the data, including kids who were improved in the failure category, nevertheless this was applied across both arms of the study. So it's not applied in any biased fashion; it's applied to both arms.

CHAIRMAN CRAIG: Okay, thank you. Dr. Wald.

DR. WALD: I just wanted to comment that right now, in the month of November 1997, if we did tympanocentesis on the children who come to the Children's Hospital of Pittsburgh with acute otitis media, all comers, 50 percent of them have an S. pneumoniae that's resistant to penicillin -- again, about half of them highly resistant.

And we've all -- the committee has expressed a discomfort in the use of this drug for resistant pneumococci, but in fact, the practitioner doesn't know whether the child has resistant pneumococci; the treatment is empiric. So is there some inconsistency in that?

CHAIRMAN CRAIG: To me, I mean, I think what it tells us is the next question -- is what should they do in phase 4 studies -- is they need to get some data with resistant organisms to be able to make that

claim. But there are a lot of other drugs that are out there.

The oral cephalosporins that are also used blindly in those same situations that also probably don't work. And there's even studies using double punctures to even show that they don't work. So I think the physician that's out there doesn't have a lot of good idea of really what is truly going to be effective with resistant organisms.

Dr. Dowell.

DR. DOWELL: Yes, I just wanted to agree with exactly what you said. I think the concern that I had that I thought I was hearing before was that the proposed labeling was for resistance pneumococci, and the concern was that we hadn't seen enough evidence that it was effective against resistance pneumococci.

But having said that, given the other 13 drugs that you have to treat otitis media, to me this looks like the best one for non-susceptible pneumococci.

So there's a big difference between saying this shouldn't be labeled as an effective drug for resistant pneumococci and saying it's not good against resistant pneumococci because it looks like among what we have, it's probably up there among the best, if not

the best.

CHAIRMAN CRAIG: Dr. Reller.

DR. RELLER: The committee voted the way it did based on efficacy and safety, although there were clearly concerns about efficacy in that as yet, not quite fully defined, penicillin resistant. I want to ask Dr. Wald a question.

Do you think -- you voiced concerns about the widespread, primary use of this agent for acute otitis media. If there were inclusive labeling that included right off-the-bat, penicillin resistant pneumococci, do you think that would encourage its use as opposed to leaving it off to put a little break on the process?

DR. WALD: You're saying if it was given in indication for resistant pneumococci -- which of course we couldn't do because we felt there wasn't adequate data --

DR. RELLER: Right.

DR. WALD: -- but if it was, would it increase usage? Sure.

CHAIRMAN CRAIG: Dr. Giebink.

DR. GIEBINK: Again, I would point out the fact that the practitioners are using a fair amount of cefixime and ceftabuten, and perhaps includes

cefpodoxime and cefprozil in that, tells me that they're not thinking bacteriologically about the middle ear.

So I think to go beyond that and think that a qualifier in ceftriaxone indications is going to have any effect on clinical practice, flies in the face of clinical practice as it exists today.

CHAIRMAN CRAIG: Dr. Reller.

DR. RELLER: Is there any -- in the statute's regulatory province of the FDA there have been I think, extreme concerns raised about some of the currently available agent given the reality Dr. Walk mentioned of the proportion of strains at first visit, that are apt to be intermediate or highly resistant to penicillin among the streptococcus pneumoniae isolates.

I mean, all the epidemiologic studies, puncture studies support that probability. And what point can one consider whether or not the drugs currently approved really wold meet even the barest minimal standard for efficacy? Can a drug be reconsidered? As the organisms change, can one call the question again?

I mean, that might be the most important thing that came out of this darn meeting.

DR. CHIKAMI: Difficult question. I guess if -- as we base approvals on evidence from adequate and well-controlled studies, clinical trials, in fact if they were submitted to the agency for review, evidence that, on the basis of adequate and well-controlled clinical trials that a drug may in fact, not be as effective, then we would take that information seriously and consider altering that product's labeling.

Now, it's very careful to say that this would have to be the same quality of evidence that we would base the initial approval. Whether or not we would view in vitro data for example, changing in vitro susceptibilities as the basis for making such change in labeling, is an issue that we would have to consider internally.

And again, that's not something that we have done in the past, and that would be a change in fact, how we considered these data.

CHAIRMAN CRAIG: A change in the MIC breakpoint would be one of the ways of being able to do that. Yes, Dr. Norton.

DR. NORTON: I would like to propose to question 3, since I --

CHAIRMAN CRAIG: I mean, let me just go back

to two. Was there any restrictions or any guidelines that anybody wanted to strongly put forward? Okay, seeing none, we'll go on to number 3 as: what are any issues that should be addressed in phase 4 studies?

DR. NORTON: Well, I think one was the obvious one that everybody on the committee raised, that we would like to see more data on penicillin resistant pneumococci.

The second, it seems to me that given the age data that the sponsor just showed, given the data that Scott presented earlier of the age relationship and the possibility that either a prolonged course or a higher dose which in essence would give you a prolonged course with ceftriaxone.

I wonder if the sponsor should not be encouraged to do a comparative trial of either the present dose versus a higher dose, or one injection versus two? In children let's say, under the age of three.

CHAIRMAN CRAIG: I mean, to me, compared to the comparative agent they still look about the same. Dr. Melish.

DR. MELISH: I would also like to strongly support more studies in resistant populations, and we heard before some question about whether it would be

ethical to study the pharmacokinetics, but those pharmacokinetic studies were done on people who were scheduled for tympanotomy.

And I think we're quite uncomfortable with the questions about protein binding and high level of resistance. So I would really like to see more studies of the pharmacokinetics in the middle ear, and higher doses, or children who have gotten two doses out aways. So that we can see whether a second dose is more appropriate or trying to concentrate up-front, the antibiotic and eradicate primarily.

We don't really know whether those sterile cultures were -- whether there was still persistence within the middle ear of some organisms that were causing problems later on.

CHAIRMAN CRAIG: I would second that. I think the tubes stand for a long period of time, oftentimes, so that you can get fluid out even later so that we could get samples out at a longer period of time.

And then I would also do ultrafiltration -- or not ultrafiltration, but filtration or ultracentrifugation or something so that I could actually measure free drug concentrations, so one could really get a better idea instead of just

guessing what they are, to actually have good pharmacologic data which would support that this does stay above the MIC of resistant strains for a sufficient period of time.

DR. MELISH: And it would be good for the sponsor because then he might be able to get an indication for the treatment of what's going to be a really serious problem and that is, real resistant pneumococci.

CHAIRMAN CRAIG: And again, looking at that population, maybe as Dr. Dagan did, which were patients that had failed earlier therapy or had very early recurrent disease, might be the ones that would give you a chance of getting the higher number of those more resistant organisms that would then give a chance to see if one dose of ceftriaxone is effective in those organisms.

Yes, Dr. Banks-Bright.

DR. BANKS-BRIGHT: One thing that's still bothering me is, in any of these studies when you're looking at ceftriaxone compared to one of the oral agents, were any of these studies done with directly-observed therapy of the oral agent?

I mean, I guess I would -- I don't know and it bothers me, that if Skip's information is right --

which I'm sure that it is just from practical experience -- that the children generally don't get all the doses of the antibiotic, what would the data look like if you were to compare -- I mean, I guess what I'm getting around to is that ceftriaxone, even -- you know that that child is getting that drug, but were any of the other studies looked at with directly-observed therapy knowing that that child for ten days, that amoxicillin three times a day or ceclor or whatever --

CHAIRMAN CRAIG: Directly observed by the mother.

DR. BANKS-BRIGHT: Yes. Because with respect to compliance, all you're asking -- you're asking the mother, did you give the drug?

DR. SOLSKY: And also the vials themselves when they were returned, so we did --

DR. BANKS-BRIGHT: Okay.

CHAIRMAN CRAIG: So people have to be very devious if they're going to try and not do it. Pour it out. Okay, any -- yes?

DR. SORETH: I wanted to make a comment about a question that Dr. Reller asked and Dr. Chikami responded to, which was the reconsideration when it appears that a drug is not working as well as it might

have been at the time of licensure.

And two drugs that have come up a lot in presentations today are cefixime and ceftabuten. If you look back at both of those labels -- and suffice it to say that there may not have been 100 percent agreement internally on approving those drugs for treatment of acute otitis media -- nevertheless, if you look at the specific labels that those drugs have, they very clearly state that the drug didn't cover children with acute otitis media due to strep pneumoniae.

Now, we can also made the evidence statement that a lot of physicians don't read the package inserts to any great extent. And so then what we're left with is really what happens in terms of the practice of advertising or promoting or peddling a drug.

And although we try to have some input as to how that happens, nevertheless, I think that there may be some disconnect between the detail of what is written on a label and what gets peddled or detailed in a physician's office.

So that when we ask the question of the committee -- and it's a tough question -- are there recommendations that you could make regarding the

appropriate use of this drug -- we're really talking about what we could or should put in a label, because that's what's going to form the basis for promotion of this drug or any other drug. And it's a very important issue.

CHAIRMAN CRAIG: Dr. Reller.

DR. RELLER: I'd like to follow up on Dr. Soreth's comments and in the context of additional studies, raise this question. The data that we had presented today showed single dose ceftriaxone to be at best, comparable to, but certainly not data to support better than the commonly used oral agents that were studied as comparators.

What would be the utility of this agent studied -- given some of the concerns about issues of oral agents, other cephalosporins versus this particular one -- what if studies were done, appropriately designed, that included some of the agents about which questions have been raised, and it turned out that they were substantially less effective than single dose ceftriaxone for acute otitis media?

Realizing the better than half of the etiologic agents isolated -- at least half or more than half -- are streptococcus pneumoniae, and as many as 30 to 50 percent might be intermediate or reduced

susceptibility to penicillin.

Is it within the realm of probability that drugs might be reconsidered based on such carefully designed files? Looking at it from the other side. I mean, all of the material we're presented is, is it as good as the comparator? What if the comparator that's licensed is substantially less good than an agent that has been shown to be equal to the best oral agents?

DR. CHIKAMI: I think one of the issues that this speaks to is, what is the role of randomized controlled trials and what sort of inference do we draw from them? I think it's always difficult to compare across studies or to make determinations about absolute response rates in any disease characteristic, which is one of the reasons why we design controlled trials.

So that within an internally valid study we can make some inference about the two agents that are being tested. So if in fact, a comparator arm which is approved, performs less well than the investigational agent, we can certainly draw the conclusion that the investigational agent in this comparative trial is better than the active control arm.

Whether or not it's reasonable to then make the inference that the active control arm, because it was beaten, is less effective than it might originally have been, I think is a trickier inference to draw. And I think that's the quandary we're in, in terms of trying to make absolute determinations about efficacy from a controlled trial.

CHAIRMAN CRAIG: To me, the whole question comes as, what do you call resistant and what do you call susceptible? That if you look at susceptible pneumococci, even nowadays, you would find that the old drugs are just as efficacious as they were in the older days. It's for the resistant organisms where we're seeing the problems.

So that if you start giving claims to the others for resistance, you bring down the crazy breakpoints which were based on urinary tract infections, not really for pneumococci, for many of the other drugs. Then one starts to create a more even playing field that tends to be based on the data.

So, but that's getting off some of the topic. Did you get enough from the question of other tests that people would think would be needed?

DR. CHIKAMI: Yes, I think so. I think we got a good feel for what the committee is concerned

about.

CHAIRMAN CRAIG: Okay. So that ends this session on ceftriaxone and we'll have a 5-minute break. Five minutes. And we'll start immediately on the next one.

(Whereupon, the foregoing matter went off the record at 2:02 p.m. and went back on the record at 2:15 p.m.)

CHAIRMAN CRAIG: As we move on you see even our breaks get shorter; only ten minutes, the next one.

The issue for part 2 of this session is on Ofloxacin Otic for treatment of otitis externa, chronic suppurative otitis media with perforated tympanic membrane, and acute otitis media in pediatric patients with tympanotomy tubes.

And we'll start off here with the presentation by Dr. Charles Myer on ENT perspective on treating localized ear infections. You're listed for 45 minutes.

DR. MYER: It shouldn't be that long. When I was asked to do this, really the charge was to talk about the child who has a draining ear and how do you treat it on a clinical basis? Because that really encompasses the issues that we're dealing with the

proposed drug this afternoon.

The potential causes of otorrhea really, are varied, and the things that we're going to be talking about today really are external otitis, myringitis -- which in a sense is a subset of external otitis when it's really just the drum involved, otitis media -- we're really talking about otitis media either through a patent ventilating tube or through a perforation, and this can either be acute or chronic and we'll divide those as we go along.

And then other causes of otorrhea which we'll enumerate but which we will not really cover. It's important to understand as a clinician, what those other causes might be because they need to be identified so that one doesn't proceed down a path of treating what one thinks is chronic suppurative otitis when in fact, another condition actually exists.

When we're talking about external otitis we're really talking about purulent drainage that one sees from the external auditory canal. This is an example where you can see some irritation and excoriation at the lateral aspect of the ear canal, and in this particular child you see some inflammation behind the ear of periauricular cellulitis which would be indicative of a severe infection.

What I want to do is just divide up otitis externa and otitis media so that those of you who don't necessarily see these children on a regular basis have an understanding of what the difference particularly is.

Typically in otitis externa -- it's known as swimmer's ear, usually seen more in the summer -- as opposed to an acute otitis or otitis media with effusion -- I'm not necessarily differentiating these at this point, but that's more of a winter and spring disease. Fever is relatively common in children who have acute otitis but uncommon in external otitis unless there's a periauricular cellulitis.

Pain is more often seen in external otitis from manipulation of the ear itself, and with children who have acute otitis it's more the deep type of pain that one may be familiar with in treating those children.

The ear canal is abnormal in external otitis as opposed to normal, with acute otitis or OME. The eardrum may be reddened with external otitis if you have a secondary myringitis as well, whereas in the child who has acute otitis or an OME, you may see changes that would be reflective of the fluid medial to the tympanic membrane.

Pneumatic otoscopy should be relatively normal in the otitis externa, as opposed to abnormal in the child who has middle ear fluid. Discharge is going to be present generally in children who have an external otitis, but will only be present in the perforated tympanic membrane or that child who has a middle ventilating tube with purulent discharge in the patient with an otitis media.

Adenitis would be relatively common in children with severe external otitis as opposed to OME, and then the hearing will generally be preserved in otitis externa as opposed to those children who have middle ear fluid.

So I think that you can see the difference hopefully, in the signs and symptoms in these two conditions -- otitis externa and then really middle ear fluid which I've not really separated into acute otitis or OME because I think we're trying to really talk about otitis externa in this session.

When we have otitis externa we need to think about what our treatment considerations might be. I put down antimicrobial drops, and I think that this is a whole host of things that are currently available and will probably be discussed as the afternoon continues.

I personally, and I don't think most clinicians think that there is "a great deal of difference", between many of the drops and one uses what one becomes comfortable with. Many of the ocular preparations have been used by clinicians -- and again, this is a presentation that is aimed at, what is the clinician doing today, and that was my charge.

And many of the clinicians will use ocular drops -- either tobramycin drops or garamycin drops -- even though there's not an indication necessarily, for the treatment of otic disease; that is what is done.

Then one often will use one of the combination drugs that is marketed for otitis externa or for external ear inflammation.

Suctioning and debridement I think, is important in those children who have severe disease. In other words, if you look in and you see a little bit of debris, oftentimes the drops will be very effective. However, if one has a severe infection where the entire, external auditory canal is -- there's a large amount of debris within the external canal -- to think that the drops are actually going to get is probably not a realistic concept.

So in that situation, cleaning the ear is often important. As an otolaryngologist I'll often

see those children who are managed by the primary care physician who didn't get better. The majority of kids will get better simply with the antimicrobial drops, but when they don't then clearly, suctioning and debridement is important.

Oral antimicrobial therapy is often used arbitrarily if there's a surrounding periauricular cellulitis as you saw in one of the previous slides. Though the most common organism is going to be Pseudomonas aeruginosa and the oral drugs that we use typically aren't effective for that, the clinician tends to use one of those agents that is effective against otitis media.

And I'm not going to explain the rationale or lack of rationale for that, but it seems to help with getting rid of some of the surrounding cellulitis.

And then lastly, if the cellulitis is quite severe, then admission and intravenous antimicrobial therapy generally after culture and with an anti-Pseudomonas agent, would be effective.

Sometimes one is put in the position of trying to differentiate between a severe, external otitis with periauricular cellulitis, and a mastoiditis, and it's difficult to do that because of

the swelling within the ear canal that prohibits examination of the ear drum. And in that situation, almost always those children are going to be admitted for intravenous therapy.

Malignant external otitis is a condition seen more in the immunocompromised group, and something that we really don't need to spend a lot of time on today. Suffice it to say that as a clinician, if one has a patient who has diabetes or who is immunocompromised either because they were born that way or we made them that way following chemotherapy, then the potential for malignant external otitis is certainly going to be higher.

Myringitis is, as I said, inflammation of the tympanic membrane itself, and in this case suctioning is going to be necessary to make the diagnosis. The ototopical drops -- oftentimes using steroids because most of what one sees is inflammation of the tympanic membrane -- may be very important, and oftentimes clinicians will use boric acid or acetic acid solutions to irrigate the canal to try to return the canal to an acidic pH, as that oftentimes will resolve the problem.

My first postulate of pediatric otology is with a child with a perforation or a patent tube, you

don't have otitis in the absence of otorrhea.

And though this may seem self-evident, I see at least two or three kids a day who come in because they were seen by their primary care physician and told that they had an otitis, they had a patent tube or perforation but no drainage, and then they were placed on oral antimicrobials and ear drops. And they come in irate that we did this procedure -- surgical procedure -- to cure the ear disease, yet they continue to have ear infections.

So I think that for most otolaryngologists and hopefully most primary care physicians, one should realize that if you have a patent tube in place, in general, if there's not drainage there's not an infection and those kids need not be treated.

And I think as we discussed a little bit today about the inappropriate use of antimicrobials and the concern for resistance, it's important that we understand when otitis exists and when it doesn't exist. And though there can be a lot of argument maybe, when you have a child who has an intact drum and you're basing your exam on some clinical factors, if you've got a tube or perforation, it would be hard to have an otitis without drainage.

So what we're talking about is this child

who has drainage coming out of the ventilating tube as you see here. Or if this were a hole in the tympanic membrane you would see purulent discharge through the opening of -- through the perforation.

So that as a physician, I think the things that we look at are the character of the drainage, and in my mind, any draining is abnormal and generally deserves treatment.

Arbitrarily, if the child has -- well, we'll get to that in a minute -- but the duration of drainage, if the parent comes in and says they had drainage two days ago but now it's dry, I don't typically treat that. But if the drainage has been ongoing, then clearly that will be something that may influence how you treat it.

A child who has drainage for more than two months arbitrarily is defined as having chronic otitis media as opposed to an acute or a sub-acute otitis, and may carry different treatment implications. And certainly the child who has chronic discharge is one that I would culture as opposed to the child who has acute drainage.

And the amount of drainage I think, becomes important because if the child has chronic discharge where one cannot examine the ear adequately, it

becomes important that one cleanse the ear so that one knows what is going on and that what one is treating is an otitis and not one of the other conditions that we mentioned briefly earlier.

So one of the concerns that parents will have is, is bloody discharge different? And I think that the short answer is yes, and let's go over why. If it responds to conventional treatment that's fine. In other words, if in the first few days you treat the child with oral antimicrobials and drops as is the clinical standard today, it's not necessary that we see every one of those children.

However, many children are very bothered by the bloody discharge and we get frequent phone calls about that, so we see those kids, and in those children, oftentimes otomicroscopy of cleaning the ear under a microscope is very helpful, because what one might see would be a granuloma over the ventilating tube that is in the eardrum.

And in that situation, all the oral antibiotics and all of the drops that you use may make no difference at all until you remove the ventilating tube which may be acting as a foreign body. So that bloody drainage can be treated initially in the standard way, but if it doesn't respond then one needs

to do a more thorough examination, specifically to rule out the presence of a granuloma.

So that acute otitis with otorrhea through a patent tube or through a perforation often accompanies a concomitant upper respiratory infection. We generally will use -- and I put in quotes -- "ototopical therapy", because I think one should realize that none of the drugs that are currently used by clinicians are necessarily approved for use through an open tympanic membrane.

So the clinical practice is to use topical therapy for acute and chronic infections, but none of the drugs are approved for that use.

We oftentimes use oral antimicrobial therapy and as a clinician, what we generally do is if the child has an upper respiratory infection we'll frequently use an oral antimicrobial agent in addition to drops. If the drainage is not that great and the child does not have a respiratory infection we oftentimes will not use an antimicrobial agent.

We don't typically culture these kids. If it continues then I do think that suctioning can be therapeutic, but clearly if you do it every time a child has a draining ear it becomes punitive and you'll have an empty waiting room in your office.

We've gone over I think, the drugs -- or the drugs that oftentimes are associated with acute otitis, and I think that in otorrhea in the acute situation, that it is really not that much different than what has been talked about previously and the oral antimicrobial choices would be generally, essentially the same.

However, some investigators have recommended in older patients that we could use more narrow spectrum antimicrobials during the summer months when no prior treatment has been given, where the patient has not been in contract with patients with other antimicrobials, and when the community experience shows a high success rate. In other words, when you don't necessarily expect to see a resistant organism.

However, in the younger children or if a patient has severe symptoms, or if you're in a situation where there may more likely be an incidence of resistant organisms -- either because of the community or daycare setting -- then it may make more sense to use a wider spectrum and a microbial agent.

So if the drainage persists for longer than a few days arbitrarily we generally will use an oral antimicrobial. We'll usually suction that patient, and I mentioned what the oral antimicrobial agent

should be effective against, especially in those children who are in a situation where a resistant organism is more likely.

Oftentimes we'll use wicks in the ear, and I think this is something that Dr. Grundfast has talked about in the past; that my training had originally been, if you have a draining ear one of the last things you want to do is put a wick in because that will further block the drainage that's coming out.

However, I think that in most situations what the wick can do is allow your drops to more effectively penetrate and actually end up where you would like them, which is in the middle ear space.

I think it would be foolhardy to say that when you have an external ear that's completely filled with purulent material, that putting drops in are going to actually get anywhere. So I do think that the use of wicks in that situation, after suctioning, are very effective.

I don't use cultures and I don't think many otolaryngologists use cultures in the acute setting with draining through either tubes or perforations. When it persists for longer than several months then one arbitrarily then defines that as chronic otitis

media, then cultures do become important.

One thing I would like to discourage would be the clinician who doesn't have cultures available but has a patient come in with draining ears and just sticks a swab into the external canal, into all of the goop that's there, and gets a Pseudomonas and then sends the child in after several shots of an anti-pseudomonal agent because they've got a Pseudomonas otitis media.

Generally, if you're going to swab the external canal you're going to get Pseudomonas, so that if you're going to do a culture you need to make sure that what you're culturing is the middle ear drainage and not the external canal.

What about phone therapy -- is this done -- since we've been talking about, do you need to do cultures, do you need to do suctioning? And at least I think that in practice what is clinically done is, if a child has a perforation or a ventilating tube and the parent can differentiate between otorrhea and wax, that it is not inappropriate to give an antimicrobial agent and a drop over the phone.

And that is something that I think most clinicians do. I'm not advocating treating otitis media by phone in children who have intact tympanic

membranes. We're talking about draining ears where it known that the child has a patent tube or perforation, and again, this is what is clinical practice.

As we get into the chronic drainage, I'll bring up this quote from Dr. Bluestone from about 12 years ago, where he said that pediatricians don't have a good perspective about the management of chronic, purulent otitis, and they're not utilizing the expertise of otolaryngologists appropriately. And let's get into why that might be.

Well, by definition, this is drainage that is persistent for longer than two months and in my mind, otomicroscopy is mandatory because you need to assess the status of the eardrum to see whether the child has a myringitis, granulation tissue, a perforation that could be present, a cholesteatoma which we'll see is a surgical disease, whether there's a ventilating tube present, and then obtain a culture after suctioning the ear.

So that in the acute setting, arbitrary treatment is appropriate. In the chronic setting you really need a more detailed exam so that you can direct your therapy based on cultures.

So that we would suction the ear, examine, try to determine some of those other factors that I

mentioned, do a culture and a gram stain, and begin obtaining audiology or audiometric assessment, because many of the drugs that you may need to use at this point may carry potential ototoxicity. So you should have a baseline audiogram from which to work.

Could the tube be infected? And this really gets into the idea of the patient who has a granuloma over the tube, and I think the answer is yes. There are several tubes that are designed to be less -- have a lesser possibility of getting infected, but clearly the tube itself can become infected.

If you've had a tube that is in for a year, 15 months, and the child has purulent drainage -- oftentimes this has persisted for more than a few weeks -- I think that it is oftentimes the tube and not the middle ear space that is the culprit, and we'll take the tube out and start over again. So I think that one can't discount the tube as the source of the infection. And that's where I get into, is when should one consider removing the ventilating tube?

And in general that's a child who has had chronic otorrhea with a tube that has been in for -- when I say a longer period of time, this is arbitrary; it's not necessarily science -- but as you get into a

lot of this with chronic drainage and the way it is treated clinically, much of this is done more in a gestalt than necessarily by studies.

I mentioned it's important how the specimen is obtained. It's still going to be Pseudomonas the majority of the time; it can be polymicrobial; and the role of anaerobes is uncertain. In one study that was done by Dr. Kinaid from Pittsburgh, you can see that Pseudomonas predominated in these 26 patients but also we're seeing staph aureus, dyptheroids, staph avadomeras, and alpha strep.

So that in these patients, initially they've been treated almost always with a systemic oral antimicrobial, active against the beta-lactamase positive and negative organisms. Oftentimes we've used one of the top antimicrobial agents and we've done regular cleansing of the ear -- sometimes every day, sometimes every other day, sometimes as often the parents could get in.

And if that didn't work then we moved on to the second step. If it worked one would consider prophylaxis, and I'm not really going to get into the issue of prophylaxis today except to say that I think that we use much less prophylaxis than we did a few years ago.

If the drainage continues then we would generally have the patient admitted to learn home IV use. When I was in Pittsburgh as a fellow all of these patients came in and they were all in the hospital. Most of these patients are treated now at home with intravenous therapy with an anti-pseudomonas, beta-lactam drug and topical care that we described previously.

If the drainage stops, again, consideration of prophylaxis. If it continues surgical therapy -- meaning a tympanoplasty and a mastoidectomy. And in the one good study that was done from Pittsburgh, if you got to this point only about ten percent of the patients actually got down to needing surgical therapy.

Generally, oral antimicrobial therapy is going to be effective with daily care; if not that, then systemic therapy along with drops; and then if not that, surgery. But surgery is usually reserved for less than ten percent of the population.

So in summary, the therapy is going to be based on your cultural results. You may want to do CT imaging to look for some sort of a middle ear process, and then tympanoplasty and mastoidectomy as I mentioned, in refractory cases.

Why don't you just jump to surgery? Well, it certainly carries its own set of complications and medical therapy is going to be effective in the majority of situations.

When we choose an ototopical drop, remember what I said; that we generally use either an ocular preparation or an otic preparation that is not necessarily approved for use through a non-intact, tympanic membrane. That's what's done now.

Methylate for a while was used, though there was a case of mercury poisoning and death, and that's certainly not used now. There are only two places in the country I believe -- Oklahoma City and Columbus, Ohio -- where that was the standard of care. that's clearly not an appropriate drop to use at the present time.

And then we get into, how much of this is emotion, that it's okay to do, versus science. Do we have data that would support the use of these preparations through the use of a non-tympanic membrane?

So you have to remember, with the use of these drops, that they are potentially ototoxic, that it could be unrecognized that chronic drainage can cause a central neural hearing loss -- it may not be

the drop itself -- you may be getting hearing loss either from the disease or the drop in frequencies in which we don't test, and it may be that the surgery itself to cure the disease process may lead to hearing loss.

So that it is not all that clean when one looks at, are the drops the problem, the disease the problem, or could surgical therapy be the problem?

Mike Poole, who's a pediatric otolaryngologist and microbiologist, said that topical antibiotics used in infected ears with a non-intact tympanic membrane is the standard of care. Clinical evidence of ototoxicity is virtually non-existent.

So I think what we've worked down to for our treatment of acute otitis with drainage and chronic otitis with drainage, is that we used drops and parenthetically, certainly the Ofloxacin drop is used clinically by some physicians today similar to the Garamycins, to the tobramycin, to podosporin, to codisporin, codimycin -- all of the different drops.

And I think that there's not science that one is better than the other, at least in the literature today looking at least, at the drops that are on the market currently and being used in the ear. But certainly Dr. Poole's statement indicates the

current practice status.

Just so we get an idea of what other idea things that could be going on, this was reported in The New England Journal several years ago, where it was a microbacterium that was being transmitted through the method that instruments were being cleaned; whether it was actually an iatrogenic infection. So that one should at least consider acid fastimes and cultures and otherwise refractory otorrhea.

Does allergy play a role? Well, it may, but in my mind and I think in most otolaryngologists minds, if you have drainage that implies infection and needs treatment.

Cholesteatoma can be a common cause of chronic drainage due to secondary infection of the keratinizing stratified squamous epithelium, and that's why you need to do a good photomicroscopic examination so that you can determine that the patient has -- you can determine whether there's a cholesteatoma present or if it's simply drainage through a tube or through a perforation. And cholesteatoma is a surgical disease, not a medical problem.

And again, just to reiterate some of those

things that we need to be thinking about as a cause of otorrhea, not just infection within the middle ear space and mastoid, one can see retraction pockets, polyps, granulation tissue, foreign body or foreign body reaction. A nasopharyngeal tumor may lead to otitis with drainage, one could see tuberculosis, Langerhans cell histiocytosis oftentimes presents with chronic otorrhea, and external otitis which we mentioned at the beginning of the session.

This was a follow-up to Dr. Bluestone's statement in 1985; presented by Dr. Nelson in 1988 in Annals. And what you see on the left is what the experts recommended. What you see on the right is what the pediatricians were actually doing. That if they had a patient who had chronic otorrhea, only nine percent of the pediatricians would suction the ear and none did middle ear cultures.

Initial therapy included oral antimicrobials, even though we know that in chronic drainage, oral antimicrobials are not going to be effective the majority of the time; 50 percent of otolaryngologists would use a topical antimicrobial, whereas 79 percent of the pediatricians would; and most of the pediatricians would use an antihistamine/decongestant.

Follow-up for the otolaryngologists would be within two days for suctioning, whereas less than five percent of the pediatricians, and then if there was failure to improve, only 40 percent would send the child to the otolaryngologist where hopefully, these things could take place.

So as you can see, at least ten years ago and there's been no new data, there's still a wide diversity as to how an otolaryngologist will treat a child with chronic otorrhea, and how a pediatrician would treat a child with chronic drainage.

And that's the conclusion of the remarks that I have on the treatment of chronic otorrhea.

CHAIRMAN CRAIG: Fine. Thank you very much, Dr. Myer. Any questions from the committee? No, I don't see any. Thank you very much for making it very clear for everyone and staying within your time.

Now we have the sponsor presentation, Part I, by Daiichi Pharmaceuticals. So Elayne -- Dr. Lombardy. Okay, fine. Just to remind you, the first Part I has 50 minutes scheduled.

DR. LOMBARDY: Good afternoon. My name is Elayne Lombardy and I work at the U.S. Subsidy of the Daiichi Pharmaceutical Corporation as the executive director of Research and Development. I'm sure that

not all of you are totally familiar with the Daiichi Pharmaceutical Corporation and it may be useful just to say one or two words about that company.

Daiichi is of course, a Japanese pharmaceutical company which has been in existence since more than 80 years and has specialized in the field of oncology, cardiovascular, and anti-infectives. And specifically in anti-infectives, Daiichi discovered and developed in Japan, Ofloxacin -- labeled Floxin™ -- which as you know has been licensed to Johnson & Johnson in the States.

Now, the subsidiary, the U.S. subsidiary is located in Fort Lee, New Jersey, and is still quite small. The entire that are in the department includes approximately 35 people. So now, to get back to the topic of this afternoon's session, I will present to you the agenda and the speakers for the Daiichi section of the session.

And first I will say a few words for the rationale for developing Ofloxacin Otic Solution; then Dr. Mindell Seidlin who is the senior director of Clinical Development will make a presentation on design and outcomes of clinical trials.

And she will be followed by two persons: Professor George Gates, director of the Virginia

Merrill Bloedel Hearing Research Center at the University of Washington, who will make a presentation of the evaluation of otic safety; and Professor Jerome Klein, professor of Pediatrics at the Boston University School of Medicine, who will discuss the role of a new ototopical therapy in pediatric practice.

My presentation is organized as follows: first I will list the proposed indications; then I will say a few words about the rationale for topical therapy, the rationale for having selected Ofloxacin, a few words about the preclinical and safety profile of this preparation, and finally, the rationale for development Ofloxacin Otic Solution today.

The proposed indications include otitis externa in adults and children -- children meaning one year and older; acute otitis media in children one year and older with tympanotomy tubes; and chronic suppurative otitis media in adolescents and others with perforated tympanic membranes.

The rationale for topical therapy is that basically local treatment is a very logical alternative for the treatment of localized infections, particularly when the size of infection is fairly easily accessible. Local treatment ensures high

concentration at the site of infection, much higher than those concentrations achieved with systemic therapy, and to some extent this may prevent the emergence of resistance.

And finally, local treatment results in minimal exposure, which of course minimizes the risk of systemic toxicity and in children, if quinoline is justified then it allows the use of that quinoline in children without there being the concern and the worry of systemic side effect, and particularly acropathies.

The rationale for having selected Ofloxacin is that Ofloxacin has been demonstrated safe and effective in the treatment of many infections, including infections due to Pseudomonas aeruginosa. Ofloxacin has a broad antibacterial spectrum ensuring -- a wide variety of clinically important, some positive and some negative pathogens likely to be associated with the proposed indications. And again, it covers Pseudomonas aeruginosa.

Things that the Pseudomonas aeruginosa shows is not so minor because in fact, it forces physicians very often to press type of to use out-of-label preparation which are potentially ototoxic solely out of the concern that the responsible agent will be Pseudomonas aeruginosa.

And finally, Ofloxacin demonstrated in vitro efficacy against resistant pathogens. It is effective against methicillin resistant Staph aureu and penicillin resistant Strep pneumoniae. And it lacks cross resistance with other classes of antibiotics such as for example, beta-lactams.

The practical safety profile of this preparation of Ofloxacin was of course, very important to demonstrate because the intent is to use this product in the minimally small children. So we did animal studies which demonstrated low systemic exposure, no skin sensitization, no local irritation, and no local toxicity to the middle and inner ear.

Which was our highest concern because since it is not absorbed system toxicity was quite less an issue than applying for the first time a very high concentration of Ofloxacin directly against the stricture of the middle ear in a baby.

Well, encouraged by this safety profile we developed Ofloxacin -- widely developed new ototopical -- today. Well, we feel that this new preparation offers advantages over available therapy. There is no therapy and specifically, no ototopical therapy approved for use in patients with open tympanic membranes.

Yet the need is there because pediatricians generally, the typical therapy has been to treat this condition using topical application of out-of-label preparation which are often potentially ototoxic. Sometimes the antibiotic is ototoxic, sometimes the vehicle is. For example, the Cortisporin™ used in the middle ear of -- gentamicin.

So we feel that advances in the treatment of otitis externa in adults and children can be achieved with the use of this preparation. First, it is a monotherapy therapy, which is in a sense, better than combination products that are used today.

It is to be used twice a day, which is sure a convenient regimen for the parents with children going to school or going to camp. And finally, the otic safety of this preparation was demonstrated even for those patients with an undetected tympanic membrane perforation.

All other of the topical preparations to-date have restrictions with regards to use in patients with non-intact tympanic membranes.

And the advantages achieving the treatment of acute otitis media in children with tympanotomy tubes and in the treatment of chronic suppurative otitis media in adolescents and others with perforated

tympanic membranes are as follows.

First, this product, Ofloxacin Otic Solution, covers all relevant pathogens including Pseudomonas aeruginosa. And again, if this is important for others because maybe a topical preparation not convenient or easy to tolerate, this is particularly important in small children, because there is not a single antibiotic approved for use in children today that covers Pseudomonas aeruginosa.

Then this preparation to some extent in some circumstances may eliminate the need for systemic antibiotic therapy. Certainly overall reduces the need for antibiotic therapy.

And finally, we've demonstrated the otic safety of this preparation, and again, if otic safety is important for little children with acute otitis media it is even more important for those patients with a chronic suppurative otitis media because that condition is chronic and those patients are likely to have been treated in the past, re-treated in the past heavily with many courses of antibiotics, and therefore are likely to have become more sensitive to ototoxicity.

Thank you. I will now introduce Dr. Seidlin who will present to you the clinical program.

DR. SEIDLIN: Thank you Dr. Lombardy, and good afternoon. It's a pleasure to be here to talk about the clinical program for Ofloxacin Otic Solution. My task this afternoon is to describe the design and outcome of the clinical trials supporting the three indications that we have in our proposed labeling.

The indications, as you've heard earlier, are: otitis externa in adults and children one year and older, acute otitis media in children one year and older with tympanotomy tubes, and chronic suppurative otitis media in adolescents 12 years and older and adults with chronic perforations of the tympanic membrane.

This slide summarizes participation in the clinical trials program, the three indications. A total of 301 subjects were enrolled in the Ofloxacin arm of the otitis externa trials, 300 were enrolled in the cortisporin arm. And 207 adolescents and adults were enrolled in the prospective Ofloxacin arm for chronic suppurative otitis media. There were 220 historical and 63 current practice controls in that indication.

And 454 children were enrolled in the Ofloxacin arm of the two studies for acute otitis

media in children with tympanotomy tubes, and 246 children were enrolled in the augmentin arm. There were also 309 historical and 68 current practice controls in that indication.

Thus, there were a total of 962 subjects treated with Ofloxacin Otic Solution in the clinical trials program that I will describe today.

Now I'd like to turn to a discussion of the trials in otitis externa in adults and children. This of course is based on protocols 002 and 003. Two adequate and well-controlled trials were performed: one in adolescents and adults and one in children.

There are currently no known differences between adults and children in the pathophysiology or the microbiology of this infection. The dose differed in the two trials because of the volume of the ear canal.

The study design for the two trials was in essence, the same. Both were multi-center, randomized, evaluator-blind trials of Ofloxacin Otic Solution versus Cortisporin™ Otic Solution administered for ten days.

The primary endpoint was a comparison of the clinical response seen to ten days after the completion of therapy. Clinical cure was defined as

complete resolution of tenderness, edema, secretions, and exudate.

The two studies are summarized here. The dark bar is protocol 002 which is in adolescents and adults; the lighter bar refers to protocol 003, the children. There were 158 Ofloxacin-treated subjects in protocol 002; they received .5 ml twice daily for ten days. And 158 subjects were randomized for the Cortisporin™ arm and they received .2 ml four times daily for ten days.

In protocol 003, 143 children were randomized to received Ofloxacin, .25 ml twice daily for ten days, and 144 were randomized to receive Cortisporin™, .15 ml four times daily for ten days.

Populations analyzed are summarized here. I've already talked about all the subjects who are enrolled which constituted the intent-to-treat population. Of these, 126 Ofloxacin-treated adolescents and adults were clinically evaluable, and 116 Ofloxacin-treated children. And 121 Cortisporin™-treated adolescents and adults were clinically evaluable and 111 Cortisporin™-treated children.

Also 48 Ofloxacin-treated adolescents and adults were microbiologically evaluable and 45

children; 50 Cortisporin™-treated adolescents and adults were microbiologically evaluable and 53 children.

The overall clinical cure rates in the two protocols include the evaluable subjects summarized here. Again, the dark bar is the adolescents and adults and the lighter bar, children. So 81.7 percent of Ofloxacin-treated subjects in protocol 002 were cured; 83.5 percent of Cortisporin™-treated adolescents and adults were cured.

The 95 percent confidence interval indicate equivalence with the lower bound of -12 percent and upper bound of 8.5 percent. In protocol 003, 96.6 percent of Ofloxacin-treated children were cured and 94.6 percent of Cortisporin™-treated children. Again, the 95 percent confidence interval demonstrated equivalence with the lower bound -4.3 percent and the upper bound, 8.2 percent.

So you noticed on the previous slide the cure rates were somewhat higher in children than they were in adults; in the low 80s for adults and the mid-90s for children. We considered what might be the reasons for this difference and examined several of them. The possible reasons listed on this slide are of course, speculative.

Although there were no differences in the mean symptoms between adults and children, there were some differences in the mean duration of otitis externa before enrollment, with the duration in adults in both treatment arms being somewhat longer than in children.

There were also some differences in the proportion of subjects with exacerbating as opposed to stable otitis externa at the time of enrollment, with some more of the adult subjects having exacerbating disease when they were first treated in the trial.

There were of course, differences in who administered the drugs to the subjects. In the pediatric trial the drug was generally administered by a caregiver under direct visualization. This may enable better counting of drops and better assurance that the drops indeed, entered the canal. In the adolescent and adult trial the subjects generally self-administered the drops.

There also may be some decreased penetration through the ear canal in adult men because of more hair, etc. These of course are all speculative.

These two slides -- which I know must be difficult to see in the back of the room -- demonstrate the overall microbiological and clinical

response by pathogen. The left-hand slide is protocol 002, the adolescents and adults, and the right-hand slide, protocol 003 of children.

The first thing I would like for you to notice is that the most important pathogens were pseudomonas aeruginosa and Staph aureus, with pseudomonas really predominating. And that was true in both trials.

The next thing I'd like you to notice is that there were extremely high, microbiological eradication rates for both trials in both arms; exceeding 97 percent in both trials for Ofloxacin and exceeding 98 percent in both arms for Cortisporin™.

The clinical cure rates by pathogen are also shown for Ofloxacin and Cortisporin™. They were both excellent in both trials.

This slide shows the overall microbiological assessment by pathogen. Eradication was achieved in 98 percent of subjects in protocol 002; 98 percent with Cortisporin™. And protocol 003 likewise; extremely high eradication rates in both arms: 98 percent Ofloxacin, 100 percent Cortisporin™. The number of persistence in recurrent pathogens were extremely few in both studies.

These slides summarize adverse events that

were observed during the course of the study. Again, on the left we have adolescents and adults in protocol 002, and on the right, children in protocol 003.

The incidence of treatment-related adverse events among Ofloxacin-treated subjects is about 15.8 percent of the adults studied; 11.5 percent of Cortisporin™-treated subjects experienced treatment-related adverse events. And these were not significantly different.

There were three Ofloxacin-treated subjects who experienced serious adverse events, one of which a rash, was considered treatment-related. There were two Cortisporin™-treated subjects who experienced serious adverse events. Again, one of these was considered treatment-related. It was also a rash.

I should point out that because these were the first clinical trials that we undertook with this study, we called any rash, regardless of severity, serious. So that this may be a bit of overly conservative calling of serious adverse events here.

There were four Ofloxacin-treated subjects and two Cortisporin™-treated subjects withdrawn due to adverse events. One of the Ofloxacin was treatment-related and two of the Cortisporin™ ones were treatment-related.

Turning now to the children, the incidence of treatment-related adverse events was low in both arms: 2.8 percent among Ofloxacin-treated subjects and 3.5 percent among Cortisporin™-treated subjects.

Serious adverse events occurred in two Ofloxacin-treated subjects; one of those was treatment-related, not noted on the slide -- that was a follicular rash -- and none among the Cortisporin™-treated subjects. Two Ofloxacin-treated subjects were withdrawn due to adverse events, as were five Cortisporin™-treated subjects.

The most common treatment-related adverse events are listed on this slide. There were no significant differences between the treatment arms in the incidents of any one treatment-related adverse event. The most common ones as you can see, were purutus and application site reactions. The others occurred in one percent or less with the exception of ear pain.

Our conclusions regarding otitis externa in children and adults are that Ofloxacin Otic Solution administered twice daily is as effective and as well-tolerated as Cortisporin™ Otic Solution administered four times daily.

I'd now like to turn to discussion of acute

otitis media in children with tympanotomy tubes. This is based on protocols 007 and 008.

As Dr. Myer discussed earlier, otorrhea is the key symptom in acute otitis media in children with tympanotomy tubes. Although fever and otalgia are cardinal symptoms of acute otitis media in children with intact tympanic membranes, they're uncommon in children with tympanotomy tubes.

In these patients, pathogens may access the middle ear either through the eustachian tube or through the external auditory canal. As Dr. Myer also mentioned, it's important for the physician to rule out other possible causes of otorrhea: foreign bodies, tumors, cholesteatomas, etc.

We considered several issues when designing the clinical trials program in this indication. First, no therapy is specifically approved for this indication, and placebo controlled trials were considered unethical because as you heard earlier, the usual practice is to treat patients with either oral and/or topical therapies.

Also, Pseudomonas aeruginosa is an important pathogen in this disorder but no oral anti-pseudomonas agent is labeled for pediatric use. And available ototopical and ophthalmic agents which are currently

in use and might cover this pathogen, are potentially ototoxic.

The specific objectives of this program were to demonstrate the efficacy of Ofloxacin Otic Solution against both the typical acute otitis media pathogens -- the strep pneumoniae, Haemophilus influenzae, and Moraxella catarrhalis -- as well as against Pseudomonas aeruginosa and Staph aureus.

It was also important to demonstrate both the general safety and the otic safety of the drug using audiometric measurements. The audiometric data will be presented later on by Dr. George Gates.

This slide summarizes the two studies in acute otitis media. In protocol 007, 226 subjects were treated prospectively with Ofloxacin, .25 ml twice daily twice daily for ten days. In protocol 008, 228 subjects were randomized to receive Ofloxacin, .25 ml twice daily for ten days, and 246 were randomized to received augmentin, 40 mg/kg per day, administered three times daily for ten days.

I should point out that this trial was initiated and completed before the new formulation for twice daily administration of augmentin was approved.

Protocol 007 was designed as a multi-center, open label trial of Ofloxacin, .25 ml twice daily for

ten days. Efficacy was assessed seven to ten days after completion of treatment. There were historical and current practice controls.

The primary endpoint was a comparison of cure in the clinically evaluable Ofloxacin subjects and the historical practice subjects who had a follow-up visit recorded in their chart. Clinical cure was defined as complete resolution of otorrhea; that is, dry ear.

The purpose of the historical and current practice groups was to provide a context for interpretation of the efficacy data in the prospective arm. It was anticipated that we would be able to gather data on more historical practice subjects than current practice subjects because the design allowed us to go back four years from the time when the prospective arm was initiated for historical subjects, while the current subject records were those of subjects who were treated during the interval when the prospective patients were being treated.

We felt however, that the current practice subjects were important because they might reflect more recent trends in microbial resistance and drug therapy.

As noted earlier, historical and current

practice subjects who had a record of a follow-up visit, were considered clinically evaluable. No data on treatment prescribed or adverse events were collected in these comparator groups.

Protocol 008 was designed as a multi-center, randomized, evaluator-blinded trial of Ofloxacin Otic Solution, .25 ml b.i.d., or augmentin 40 mg/kg per day in three divided doses for ten days. The primary endpoint was identical to protocol 007; that is, clinical response seven to ten days after completion of therapy. Critical cure was also defined in the same way: complete resolution of otorrhea.

The inclusion/exclusion criteria were identical for these two studies, with one important exception. And that is that subjects in whom pseudomonas aeruginosa was isolated at baseline as the sole pathogen were withdrawn from both arms of the study and were not considered clinically evaluable.

This was done because it was recognized that most isolates of pseudomonas aeruginosa would be resistant to augmentin. Subjects were withdrawn from both arms in order to protect the study blind.

The populations analyzed in the two trials are summarized here. For protocol 007, 225 subjects received Ofloxacin, record were reviewed for 309

current practices, 68 -- I'm sorry, 309 historical practice and 68 current practice subjects. And 143 of the Ofloxacin-treated subjects were clinically evaluable, and 107 of those were microbiologically evaluable.

So 218 of the historical practice subjects and 48 of the current practice subjects had a record of a follow-up and were thus considered clinically evaluable.

In protocol 008, as I mentioned earlier, 228 subjects were randomized to received Ofloxacin; 246 the Augmentin™; 140 of the Ofloxacin-treated subjects were clinically evaluable; and 146 of the Augmentin™-treated subjects were clinically evaluable. So 83 of the Ofloxacin-treated subjects were microbiologically evaluable as were 93 of the Augmentin™-treated subjects.

I wanted to show you how many were excluded from clinical evaluability because pseudomonas was isolated as a sole baseline packaging. So of the subjects in the Ofloxacin arm and 27 of those in the Augmentin™ arm were excluded from clinical evaluability for this reason.

The overall clinical cure rates in the evaluable subjects are shown here. In protocol 007,

85 percent of Ofloxacin-treated subjects were cured. This was statistically significant from the 64 percent of historical practice and 71 percent of current practice subjects who were cured. There was no statistical difference between the historical and current practice arms.

In protocol 008, 76 percent of Ofloxacin-treated subjects were cured, and 69 percent of Augmentin™-treated subjects were cured. The 95 percent confidence interval shown here indicates the equivalence for these two therapies. The low limit of the confidence interval is -3.7 percent and the upper limit is 18.2 percent.

This slide shows the overall microbiological and clinical response by pathogen in the two trials. Again, protocol 007 on the left and protocol 008 on the right. The eradication rates again, were extremely high for Ofloxacin for all of these pathogens, exceeding 93 percent in both trials.

The eradication rates for Pseudomonas aeruginosa and Staph aureus in protocol 008 were statistically significantly greater than for Augmentin™. For Pseudomonas aeruginosa, 100 percent versus 43 percent, and for Staph aureus, 96 percent versus 48 percent.

I should remind you that although patients who had a sole culture of Pseudomonas were excluded from clinical and therefore microbiologic evaluability, those who had Pseudomonas at baseline as part of a mixed culture were allowed to continue in this study and were evaluable.

The clinical responses by pathogen are also shown here. The clinical responses for the treated subjects exceeded 83 percent for all of these pathogens -- for Pseudomonas aeruginosa in this arm and Moraxella probably because of relatively small numbers. And in fact, the clinical response rate for subjects with Staph aureus, actually they're statistically significantly greater than that for Augmentin™; that's 82 percent versus 44 percent.

The overall microbiological assessment by pathogen is shown here. For Ofloxacin-treated subjects in protocol 007 and protocol 008, eradication rates were 97 and 98 percent; for Augmentin™ it was 71 percent.

Persistence occurred for two percent of pathogens for protocol 007, and 1.4 percent of pathogens in Ofloxacin-treated subjects in protocol 008. In contrast, persistence occurred for 26 percent of pathogens in the Augmentin™-treated subjects in

protocol 008.

Recurrence is not really different between the two arms in protocol 008.

This slide reviews the changes in the Ofloxacin MIC for persistent or recurrent pathogens in AOM Ofloxacin-treated subjects in these two protocols. As you've already noticed, there are only a handful of persistent or recurrent pathogens -- seven altogether.

There were two pathogens who had a one dilution change at MIC. This of course, is within the test/retest variability of most laboratories and most people would not consider this significant treatment-related emergence of resistance.

These slides summarize the adverse event experience in the two protocols. In protocol 007, 13 percent of Ofloxacin-treated subjects experience treatment-related adverse events; of these, three were serious, none of them were treatment-related. There were six subjects withdrawn from two adverse events.

In protocol 008 there was statistically-significant difference in the incidence of treatment-related adverse events, with six percent of Ofloxacin-treated subjects and 31 percent of Augmentin™-treated subjects experiencing treatment-related adverse events.

There were no serious adverse events in the Ofloxacin arm; there were two in the Augmentin™ arm. Again, none of these were treatment-related. Nine Ofloxacin-treated subjects and 19 Augmentin™-treated subjects were withdrawn due to adverse events.

The most common treatment-related adverse events in the two studies are shown here. In protocol 007 we had a smattering of different adverse events: earache, bitter taste were the most common.

Ofloxacin is well-known to have a bitter taste and it was anticipated that either because of sensitivity of the cortitympany in the ear or passage of the drug through the eustachian tube to the pharynx, bitter taste might be perceived in some subjects.

It was quite transient and didn't result in treatment, as continuation in any subjects. Other adverse events occurred less frequently.

In protocol 008 there were statistically significant differences in the incidence of three adverse events. Diarrhea occurred in one percent of Ofloxacin-treated subjects, and 27 percent Augmentin™-treated subjects. Rash occurred in one percent of Ofloxacin-treated subject and five percent of Augmentin™-treated subjects. Monilia infections

did not occur in any Ofloxacin-treated subjects, in seven Augmentin™-treated subjects.

The conclusions drawn from these two protocols are that Ofloxacin Otic Solution is superior to Augmentin™ in eradicating Pseudomonas aeruginosa and Staph aureus. Ofloxacin is as effective in Augmentin™ in eradication of strep pneumoniae, H. influenzae and M. catarrhalis in this indication.

Ofloxacin is clinically equivalent to Augmentin™ in the treatment of AOM in children with tympanotomy tubes when children with sole cultures of Pseudomonas aeruginosa are eliminated. Ofloxacin Otic Solution is associated with fewer treatment-related adverse events than Augmentin™, and it provides effective, empiric coverage thus, for all pathogens associated with acute otitis media in children with tympanotomy tubes.

Ofloxacin Otic Solution is thus safe and effective for the treatment of acute otitis media in children with tympanotomy tubes.

Now we'll turn to a discussion of chronic suppurative otitis media in adolescents and adults.

Chronic suppurative otitis media occurs in patients with chronically perforated tympanic membranes. It's characterized by chronic or

intermittent otorrhea and many of these patients develop chronic, middle ear pathology.

Pathogens may access the middle ear, either from the eustachian tube or from the external auditory canal. It is of course, important for the physician to rule out other causes of otorrhea as was mentioned earlier: cholesteatoma, tumors, other mastoiditis, foreign bodies, and so on.

A single, open label study was conducted in this indication because no comparative agent with labeling for this indication exists. The similarity in the pathophysiology and microbiology of this infection to that of acute otitis media in children with tympanotomy tubes supports the notion that the trials in these two indications should support each other.

Finally, there are relatively few subjects with chronic suppurative otitis media and perforation in the United States. This is due at least in part, to aggressive therapy to acute otitis media in childhood. Inadequate treatment of acute otitis media in childhood is the most common reason for chronic perforations in most parts of the world.

In addition, the prevalence of tympanoplasty -- that is, repair of chronic perforations -- again,

further reduces the subject populations that was available to us.

This study was a multi-center, open label trial, very similar in design to protocol 007. Subjects were treated with Ofloxacin, .5 ml b.i.d. for 14 days. Efficacy was again assessed seven to ten days after completion of treatment. Historical and current practice controls similar to those in protocol 007 were used.

Again, the primary endpoint was a comparison of cure in the clinically evaluable Ofloxacin-treated subjects, and the historical practice subjects with a follow-up. Clinical cure again, was defined as complete resolution of otorrhea.

The populations are illustrated here: 207 subjects were treated with Ofloxacin; 162 of these were clinically evaluable; 99 of these were microbiologically evaluable. Records were reviewed for 220 historical and 63 current practice subjects; 185 of historical and 54 of the current practice subjects had a record of a follow-up visit.

The overall clinical cure rate in Ofloxacin-treated subjects were 91 percent. This was significantly greater than the cure rate in the historical practice subjects and the current practice

subjects which were 67 percent and 70 percent, respectively. Again, there was no statistical significance between the historical and the current practice groups.

The most common baseline pathogens isolated in microbiologically evaluable subjects are listed here. Pseudomonas and staph aureus were the most common, followed by proteus mirabilis and an assortment of other enteric organisms. One hundred percent of pathogens isolated in this protocol were eradicated.

The adverse event experience for this trial is summarized here. There were 23 percent of subjects who experienced treatment-related adverse events. None were serious. There were five subjects withdrawn due to adverse events.

I should point out that in this trial subjects were asked to record on a patient diary whether they experienced bitter taste after the first administration of Ofloxacin and this was considered a treatment-related adverse event. The bitter taste was transient and didn't result in discontinuation of therapy in any subject.

The most common treatment-related adverse events are listed here. As we expected, bitter taste

-- taste perversion -- occurred in 17 percent of subjects and was the most common treatment-related adverse event. Dizziness and Pruritus occurred in two percent of subjects, and the other events occurred in a smaller proportion of subjects; thus, the adverse event profile was quite benign.

Our conclusions regarding chronic suppurative otitis media in adolescents and adults with chronic perforations of the tympanic membrane are that Ofloxacin Otic Solution is effective in resolution of otorrhea and eradication of the relevant pathogens.

Transient bitter taste is the most common treatment-related adverse event and is transient and did not result in treatment discontinuation. Ofloxacin Otic Solution is well tolerate with no serious adverse events and is thus safe and effective in this indication.

At this point I'd like to turn the discussion over to Dr. George Gates from the Virginia Merrill Bloedel Hearing Institute, University of Washington. He will discuss the otic safety of the solution. I think I've forgotten that you may have wanted a break at this point.

CHAIRMAN CRAIG: We did have a break. Is

the remainder only about ten minutes for both?

DR. SEIDLIN: Maybe 15.

CHAIRMAN CRAIG: Fifteen? How long is the next one going to be?

DR. SEIDLIN: I think Dr. Gates is about ten minutes.

CHAIRMAN CRAIG: Yes. Why don't we go ahead -- five minutes -- go ahead and get that one done.

DR. GATES: Thank you, Mr. Chairman, members of the panel, members of the FDA staff. I appreciate going ahead. There's a chance I can get back to Seattle tonight, so I appreciate your forbearance.

I'm a otolaryngologist at the University of Washington. I spend half my time taking care of patients and the other half doing research, and I'm delighted to be here to talk about the safety of this agent.

As Dr. Seidlin has pointed out with the efficacy, it's my privilege to review the safety data with you. This is professionally exciting to me because in 30 years of practice this is the first agent that has demonstrated both safety and efficacy when placed in the middle ear, and if you approve it, it will be the first agent approved for use in this important area.

Over three-quarters of a million children every year in the United States have tubes put in their tympanic membranes to treat chronic otitis media effusion or recurrent acute otitis media. The principal complication of tubes is otorrhea -- pus coming out through the tube.

This engenders substantial health care costs as well as anxiety on the part of the patient and the parents to have all this foul stuff coming out their ears. And one-third of kids with a tube will develop infection at some time, and most tubes stay in seven to 12 months, and with the long-term tubes, every child is going to experience it at least once.

Currently, we have no approved agent for treatment of this condition so we go ahead and treat it with unapproved agents. And ototopical medication, as was pointed out very nicely by Dr. Myer, is a key element in the treatment of the otorrhea.

The otorrhea may be due to acute otitis media coming through the middle ear and out the tube, or it may be due to water contamination through the tube into the middle ear. The net result is the same, of mucositis of the middle ear.

Most of the agents contain aminoglycosides. Some of them contain other agents such as propylene

glycol, which is known to product cholesteatoma in animals, and yet we've had to put this in the ears of patients.

The animal toxicity shows both auditory and vestibular toxicity from aminoglycosides. The point was raised earlier: is this important in clinical practice? While the incidence of proven complications from aminoglycoside therapy in the middle ear is small, it is not zero.

And we know from animal data that when drops are put in the middle ear we can see some damage to the hair cells in the basis turn of the cochlea, and functional hearing tests with auditory and brainstem responses demonstrate loss of hearing in the high frequencies.

I'd like to quickly summarize two studies that were done to assess Ofloxacin in the middle ear. Dr. Barlow and myself and our colleagues evaluated guinea pigs who had Ofloxacin one percent -- three times the usual dose -- placed in the middle ear for seven days by a subcutaneous catheter.

Schaefer of Michigan looked at two different doses with longer-term therapy. The Schaefer data with 0.3 percent had histology and showed absolutely no effect on the mucosa and the ossicles. That

includes the joints which are cartilaginous joints, although they're not weight-bearing. There's no evidence of cartilage pathology or bone pathology in these joints.

And in the inner ear there was no effect on the auditory brainstem response and no effect on the morphology of the cochlea.

Here's a cartoon that shows you a little bit of the anatomy of the cochlea which is not familiar probably, to most of us. The inner hair cell is the sensory cell; the other hair cells are, as we've learned in the past ten years, are little micromechanical motors that amplify the sound energy and somehow transmit it to the inner hair cells.

Loss of either the outers or the inners results in hearing loss, and in order to demonstrate this histologically we remove the tectorial membrane and take this whole block of tissue, put it on a slide, and look at it from top downward so we can see the supporting cells, the hair cells, the pillar cells, in the next slides.

Here we see on the left, one of our animals with a one percent solution. Here you see the inner hair cell cilia standing up straight and tall -- the normal pillar cells. And the three rows of outer hair

cells with a nice, normal V-shaped configuration.

Contrast this to the Cortisporin™ animals that were -- the dose was administered in the same way. There's a little bit of a clumped hair cell but basically in this section, all the hair cells have been wiped out by the Cortisporin™ agent.

And as we see in this summary graph, saline controls have only about one percent hair cell loss; the Cortisporin™ 65 percent; Gentamicin about eight percent; the Ofloxacin one percent -- the same as saline. The vehicle, benzalkonium, was studied in two strengths as well, and the vehicle is also non-ototoxic.

These are the auditory brainstem response in the animals. As you know, you can put clicks in the ear of an animal and record the vertex EEG and summarize it, and infer from this the sensitivity of the ear. This numbers represent the change from baseline in vehicle -- and notice less than -- the average was about five decibels; we consider a ten decibel change as significant.

With 0.3 Ofloxacin, again essentially no change. One percent we have this anomaly here -- one animal out of seven who experienced about a 40 decibel change at day 14, and this had come down to 25

decibels at day 28. But with the group data you see this averages out, so it's almost all of them within the normal range for the group, with the exception of that one animal.

Contrast this to the neomycin where there's an average 40 db shift that is permanent -- doesn't change from day-14 to day-28, and involves all the test frequencies.

So the animal studies can be summarized to demonstrate the lack of local irritation in spite of high levels of the drug, and lack of adverse effect on the mucosa and the ossicles, as well as the structure and function of the inner ear.

Now, we want to review quickly the audiometry data from protocol 008, and that's acute otitis media in children with tympanotomy tubes. All the subjects were over four; no existing hearing loss, sensoneural loss; and testing with behavioral audiometry was conducted prior to therapy and at their final visit where there was failure or test-of-cure.

Testing for air and bone was done at 500, 1000, 2000, and 4000 cycles. Testing of air conduction also was done at 8,000. Again, a change of ten decibels is the minimum, clinically-significant change, and this is a conservative change. The data

are presented as an average of the thresholds at the three speech frequencies.

We also looked at 4,000 and 8,000 and there's essentially no change in these children. A positive change represents improvement and a negative change as worsening.

And the target ear is the ear with the disease or if both ears are affected it's the more severely affected ear. For bilateral cases, if both were equivalent, the right ear was the target ear. And audiometry was available for all the subjects in the study.

Here we see the bone conduction puratone average for Ofloxacin and for Augmentin™, and none of them worsened in bone conduction; most stayed the same; and there was one subject in each that showed a slight improvement over the test/retest time.

Here we see the data from the air conduction which involves passage through the middle ear, and the results are somewhat different. Obviously if the middle ear effusion is present it's going to cause a loss of air conduction which will tend to improve as the ear improves.

And this shows in fact, that was the case: 68 percent of the target ears showed an improvement in

the Ofloxacin group; and in the Augmentin™ group, 35 percent and 24 percent of the target and non-target ears.

Now, one subject showed a decrement; here we have one in the non-target ear and two in the target ear that showed a decrement in the air conduction. Remember that the bone conduction was unaffected.

So we conclude that Ofloxacin Otic 0.3 percent solution is not associated with changes in the ossicles or the structure and function of the inner ear in the guinea pig, and it did not adversely impact on hearing in children in protocol 008.

We should mention that we were not able to do vestibular testing in this age group, but none of the subjects exhibited any of the manifestations of vestibular loss, and most of the dizziness that was encountered was transient from cold solution in the warm ears which creates a thermal effect.

Thank you very much, Mr. Chairman.

CHAIRMAN CRAIG: Thank you. Jerry, why don't you go on? We'll to the last one as well.

DR. KLEIN: My role is to discuss the pediatric issues and the remarks will be brief.

The current usage of ear drops in pediatrics is for the three indications that were evaluated. It

is: otitis externa; otitis media that evolves to a perforation and then drainage following that perforation; and the extensive concern now with the placement of ventilating tubes and otorrhea that follows a child who has had ventilating tubes placed.

The available preparations are used extensively. They include Cortisporin™ which is a dual antimicrobial preparation -- polymyxin B and neomycin and hydrocortisone; Coly-Mycin™ S -- which is only neomycin and hydrocortisone; and the two ophthalmic preparations, Tobradex™ -- which is tobramycin and dexamethasone -- and Garamycin™, which is gentamicin alone.

I should add that there is an acidic acid preparation, VoSOL™, that is used with or without hydrocortisone, but because of its acidity is often a painful preparation for the child because of the irritated, external ear.

The concerns have been expressed of potential ototoxicity and there are extensive animal data relevant to the use of aminoglycosides, but I think the usage has been so extensive over so many years that if it was a significant clinical problem it probably would have been recognized. So it's a potential ototoxicity.

The limitation on usage in children with perforations I took from the package insert for Cortisporin™ and the quote is, "Should be used with care when the integrity of the tympanic membrane is in question". And of course, this is most of the time.

Finally, the drops have to be administered three or four times a day; that may be an imposition or burden on some children in daycare or school-age children.

To look at the two issues subsequent to otitis externa specifically and how they evolve -- and I think some of this has been related and I'll go over it rather quickly -- some acute otitis media will progress to perforation because the abscess contents is such that the tympanic membrane bulges; there is ischemia of the tympanic membrane centrally; and perforation follows.

The membrane is so vascular that usually it heals quickly -- sometimes with in a day or two -- but on occasion it persists. If the abscess has drained completely and there is no further inflammatory reaction of the mucus membrane, that may remain dry after several days and then the perforation may seal.

But in some cases there will be a mucoytis with persistent ear drainage, and the mucoytis -- the

results of an ear drainage might be due to organisms aspirated from the nasopharynx or from the external ear canal. So the range of pathogens is inclusive of those two sites.

Management includes eardrops, daily cleansing of the ear canal -- although this is infrequently done in pediatric practice -- and there's considerable use of oral antimicrobial agents, particularly amoxicillin, sometimes Augmentin™, or trimethoprim-sulfamethoxazole. As has been pointed out, that would be suitable for the organisms aspirated from the nasopharynx, but inadequate for those organisms that are from the external canal.

Some children will develop local tissue invasion, cellulitis, possibility of mastoid involvement, and they will need the regimen mentioned by Dr. Myer of parenteral antibiotics and perhaps surgery. The surgery may include mastoid surgery or subsequently, the replacement of the tympanic membrane -- repair of the tympanic membrane.

The tympanotomy tube story is very similar. We're replacing the perforation now with the orifice of the tube. And this is just a diagram from the book that Dr. Bluestone and I have written. And the tube is placed after an incision and then with forceps the

tube is placed in that incision and remains for an average of eight to 12 months.

Dr. Gates mentioned the many tubes that are in use currently every year. My bet would be that this number will increase as the concern about resistance developing following chemoprophylaxis diminishes -- the use of chemoprophylaxis for recurrent episodes of acute otitis media.

I should have mentioned that the two reasons that children are referred to an otolaryngologist for placement of ventilating tubes are persistent middle ear effusion -- particularly if associated with hearing impairment -- and the child who has previously failed chemoprophylaxis in prevention of new episodes in recurrent acute otitis media.

But as we put limits on chemoprophylaxis, it's likely that the number of procedures for placement of tympanotomy tubes will increase.

The tympanotomy tubes work. They do diminish the number of acute episodes, they serve to ventilate the middle ear space, and with that ventilation one now has an air-filled rather than a fluid-filled space, and restoration of the hearing impairment that had been associated with the conductive loss when the fluid was present.

It also serves to allow drainage from the mucous membranes so that an abscess is essentially not formed with an acute infection. But the protective function of the tympanic membrane is lost, so now you have the tube and it allows for contamination by organisms in the ear canal, as well as reflux of organisms from the nasopharynx.

So the pediatric interest is summarized in the final two slides. This is an agent that is affected against both organisms in the nasopharynx, as well as those that are derived from the external ear canal, and you can see the microbiologic eradication rates for those two sets of organisms.

I'm impressed with the extent of the studies that have been performed; I think they probably are the largest studies for each indication available in the literature and when published will be a substantive contribution to the literature. And I think they do demonstrate clinical efficacy and safety for each indication.

Less concern for ototoxicity; that's the vague concern about the aminoglycosides. And I think the fact is that we haven't had a lot of pediatric experience in randomized control trials, and this is a substantive contribution to the pediatric

literature.

Finally, these are modest administrative points but b.i.d dosing is easier than t.i.d. or q.i.d. I think one of the bonuses that may occur is the frequent usage of oral agents -- both for the chronic event following acute otitis media as well as the otorrhea that follows tubes -- may be one of the ways that will diminish the total volume of systemic antibiotic usage.

And finally, it removes the barrier or restrictive statement that is currently in the package inserts for other products. Thank you.

CHAIRMAN CRAIG: Thank you, Dr. Klein. Any questions that people are going to have we might give to them right now and then they can respond after the little 10-minute break. Are there any specific questions of the sponsor from any of the members?

DR. AZIMI: On protocol 008, clinical response and microbiological response with regards to Staph aureus was so low when Augmentin™ was used. What might be the explanation for that? The response was lower than expected for some other organisms -- Haemophilus -- but generally in the ballpark of what we've seen with treatment of otitis media. But for Staph it was particularly low.

CHAIRMAN CRAIG: You mean, for the Augmentin™ or for --

DR. AZIMI: For the Augmentin™.

CHAIRMAN CRAIG: For the Augmentin™, yes. For the comparative agents --

DR. AZIMI: Their product looks very good.

CHAIRMAN CRAIG: We'll take a 10-minute break, and so I have right now by my watch it's quarter-to, so in ten minutes, at five-minutes-to we will start again.

(Whereupon, the foregoing matter went off the record at 3:46 p.m. and went back on the record at 4:03 p.m.)

CHAIRMAN CRAIG: The next part of the program is the FDA presentation by Cheryl McDonald.

Was there any response to the question -- that's right, I forgot about that.

DR. SEIDLIN: None of the Staph aureuses in protocol 008 Augmentin™-treated subjects were resistant at baseline, so that is not the explanation. The other thing I just looked at was to see how many of those Staph aureuses were part of the mixed infection at baseline.

Now, I can tell you that some ten percent -- I'm sorry, 40 percent -- that is, ten of the Staph

aureuses that were isolated from Augmentin™-treated subjects at baseline were part of a mixed infection. I don't know offhand if those were the failures. So that might be part of the explanation.

CHAIRMAN CRAIG: Okay. Thank you very much. Dr. McDonald.

DR. McDONALD: Good afternoon, ladies and gentlemen. I'm Cheryl McDonald. I'm a medical officer from the Division of Anti-Infective Drug Products and I've been the primary medical reviewer on the Ofloxacin Otic NDA. And this afternoon I'd like to present the results of my review of the NDA, highlighting those areas where I had differences of opinion between my results and the applicant's.

As you've heard, this application has three clinical indications for which labeling is requested: otitis externa in adults and children, acute otitis media in children with tympanotomy tubes, and chronic suppurative otitis media in adolescents and adults with perforated tympanic membranes.

There were five Phase 3 clinical studies presented to support these three clinical indications. For otitis externa there were the two studies: protocol 002 in adults and protocol 003 in pediatric subjects.

For acute otitis media in children with tympanotomy tubes there were two studies: protocol 008 which was a randomized, evaluator-blinded study using an active comparator, Augmentin™; and protocol 007 which was an open label trial with historical and current practice controls.

And for chronic suppurative otitis media there was one study, protocol 006, in adolescents and adults.

What I'd like to do is review each study on an indication-by-indication basis in the sequence that you see here, starting first with protocol 002.

Protocol 002 was the study of otitis externa in adults -- adolescents actually, and adults, but for ease of speaking I'll say adults. This was a multi-center, randomized, evaluator-blinded trial pitting Ofloxacin versus Cortisporin™ Otic solutions, each for ten days. The age of the subjects was to be greater than or equal to 12 years and they were to have a diagnosis of acute otitis externa.

And in this study, 314 subjects were enrolled. Each of the 314 subjects received at least one dose of medication. These 314 subjects were distributed as 158 in the Ofloxacin arm and 156 in the Cortisporin™ arm. The applicant derived the

clinically evaluable population of 126 and 121 in the two treatment arms, respectively.

As I reviewed this study I made very few changes in the evaluability status or the efficacy outcome assessments of the subjects; however, during the course of the review of this NDA information came to light that necessitated the removal of some of the investigative sites. And at the final analysis of this study, my clinical evaluable population came down to 99 Ofloxacin-treated subjects and 98 Cortisporin™-treated subjects.

Looking at what these changes did to the clinical cure rates compared to the applicant's, we see on this slide the applicant showed a clinical cure rate of 82 percent in the Ofloxacin arm, 84 percent in the Cortisporin™ arm, with a 95 percent confidence interval of -12 to 8.5. And my results were a Ofloxacin success rate of 77 percent, Cortisporin™ 81 percent, and a 95 percent confidence interval of -16.3 to 8.6.

So the net effect of the changes I made were that each treatment arm showed a somewhat lower efficacy rate and the confidence interval widened a bit with the lower bound now being -16.3.

Turning to the microbiology data of this

study, there was less of an impact on the micro data for this study. A per subject basis the eradication rates were still at least 98 percent in each arm. Looking on the per pathogen basis you can see that again, they stayed quite high with all the baseline pathogens being eradicated in the Ofloxacin arm and all but one isolate of Pseudomonas being eradicated from the Cortisporin™ arm.

Looking at the people who were considered clinically and microbiologically evaluable, you can see that the success rates I derived for the Ofloxacin-treated subjects was 84 percent, which is not substantially different than that of the applicant. And the rates I derived for the Cortisporin™-treated subjects was 87 percent, versus 88 for the applicant.

So my changes did not make a significant difference on the overall clinical and microbiological success rates.

Looking at the safety results of this study, most of the adverse events were of mild to moderate intensity and there were similar rates of adverse events between the two treatment groups: 42 percent of the subjects in the Ofloxacin arm and 33 percent of the subjects in the Cortisporin™ arm experienced some

sort of adverse event.

The adverse events that were most common, regardless of the relationship to the study drug, were pruritus and application site reaction, rhinitis, earache, and headache. And these were seen with similar frequencies among the two treatment groups.

Now I'll turn to the second study of otitis externa which was the study in pediatric subjects. This study was of analogous design to that in the adult subjects with appropriate corrections and adjustments made for the subject's age. These subjects were to be at least one year of age to less than 12 years of age.

There were 287 subjects enrolled, and all of whom received at least one dose of some medication. These subjects were distributed among the two treatment groups as 143 in the Ofloxacin arm and 144 in the Cortisporin™ arm. The applicant derived a clinically evaluable population of 116 Ofloxacin subjects and 111 Cortisporin™-treated subjects.

Again, analogous to the adult study the medical officer needed to exclude some of the investigative sites and the resultant clinically evaluable population from the medical officer's perspective was 81 for Ofloxacin-treated subjects and

78 Cortisporin™-treated subjects. This was a 30 percent loss of the clinically evaluable subject in each arm.

In both of these otitis externa subjects the demographic characteristics and baseline disease characteristics of the two treatment arms were balanced, both prior to the exclusion of these centers and after the exclusion of the centers.

Looking at how the medical officer's changes affected the clinical cure rates, we see that they didn't really make much of a difference. The Ofloxacin-treated subjects had a 96 percent cure rate and the Cortisporin™-treated subjects had a 92 percent cure rate. And the 95 percent confidence interval was -4.5 to 12.4, which was not substantially different than those found by the applicant.

Looking at the microbiology of the pediatric subjects, again, on a per subject basis there was no real changes. What you see on a per pathogen basis is that we lost some of the number of isolates from some of the organisms that were seen in fewer than ten subjects. But overall, the eradication rates remained very high -- 100 percent in each arm.

Now, what we see comparing the overall, clinical and microbiological success rate in the

subjects who were both microbiologically and clinically evaluable is that the medical officer's changes did not affect the overall rates; they were very high in both arms.

Looking at the safety results we see that most adverse events seen in this study were of mild to moderate intensity. The rate of adverse events between the two treatment groups was similar: 35 percent of the Ofloxacin-treated subjects versus 26 percent of Cortisporin™-treated subjects experiencing an adverse event.

Looking at those adverse events that were most common among the treatment groups regardless of relationship to the study drug, we see that earache, otitis media, fever, rhinitis, and coughing were the top five adverse events seen, and they were seen with similar frequencies between the two treatment groups.

So when we look at the studies for otitis externa, what we see when comparing the efficacy rate is that across the board adults fared worse than children, with an Ofloxacin success rate of 77 percent in adults versus 96 percents in pediatric subjects. the success rate for Cortisporin™ of 81 percent in adults and 92 percent for pediatric subjects.

We found these results puzzling and like the

applicant mentioned, we investigated some potential reasons that we could have seen these results. We wondered if there was some difference in the baseline disease characteristics, the compliance with therapy, the use of cleaning procedures, or baseline microbiology between the adults and children.

With respect to the baseline disease characteristics -- Dr. Seidlin mentioned this -- the adults were found in a greater percent -- 75 versus 64 percent of the pediatric subjects -- to have an exacerbated condition of otitis externa at enrollment. And the adults also had a longer duration of symptomatology prior to enrollment: five days versus three days for the pediatric subjects.

And thought it was not otherwise specified, we did find that endocrine and metabolic conditions were seen in a bit higher frequency in adults: 13 percent versus peds, three percent.

Looking at compliance with therapy we found that between adults and children the compliance with the therapies in both treatment arms were similar. And the applicant provided wicks for medication administration to the investigator to be used at his or her discretion. We thought perhaps maybe the pediatric subjects had wicks used more often which

would have kept the therapy in the area of interest, but the data on the use of wicks was not captured.

Looking at cleaning procedures -- not really just abridement but suctioning could be included in that -- we found that really they were not frequently used in either of the adults or pediatrics, and actually overall, the adults had a bit higher frequency of cleaning procedures: eight percent versus pediatrics. And within each study the use of the procedures was balanced between the Ofloxacin and Cortisporin™ arms.

Looking at the baseline microbiology, more adults -- 67 percent versus 57 percent pediatric subjects -- had a baseline pathogen isolated, and in fact, a slightly greater percentage of adults -- 19 percent versus 13 percent of the pediatric subjects -- had multiple pathogens isolated at baseline.

Looking at the actual pathogens in the MIC distributions, there was no real difference between the adult subject's pathogens and the pediatric subject's pathogens with respect to the distribution of the MIC values.

So we're left with two studies in otitis externa which show somewhat different results, and this causes us to ask the committee: do these results

of study 002 demonstrate adequate safety and efficacy data to support the approval of Ofloxacin Otic Solution 0.3 percent for the treatment of otitis externa in adults?

Similarly, do the results of study 003 demonstrate adequate safety and efficacy data to support approval of Ofloxacin Otic Solution 0.3 percent for the treatment of otitis externa in children?

Next we'll move to the second clinical indication; that is, acute otitis media in children with tympanotomy tubes. The first study we'll review is study 008 which was the multi-center, randomized, evaluator-blinded study comparing Ofloxacin Otic Solution versus Augmentin™ for ten days -- Augmentin™ being dosed at 40 mg/kg per day dose.

These subjects were to be greater than or equal to one year of age and less than 12 years of age. They were to have acute purulent otorrhea with tympanotomy tubes in place -- acute being defined as less than three week's duration. A total of 474 subjects were enrolled, all of whom received at least one dose of medication.

The total enrollment is distributed as 228 subjects in the Ofloxacin arm, 246 in the Augmentin™

arm. The applicant derived a clinically evaluable population of 140 Ofloxacin-treated subjects and 146 Augmentin™-treated subjects.

The medical officer made a few changes but they didn't really result in that great a percentage of subjects being excluded from the applicant's clinically evaluable population. The resultant medical officer clinically evaluable population was 135 Ofloxacin-treated subjects and 145 Augmentin™-treated subjects. And again, the demographic characteristics and baseline disease characteristics of the two treatment arms were balanced in all of these populations.

Looking at the effect of the medical officer changes on the clinical cure rates, we see that they really didn't make a substantial difference compared to those found by the applicant. Medical officer found a clinical cure rate of 76 percent in the Ofloxacin arm and 68 percent in the Augmentin™ arm, with a 95 percent confidence interval of -3.1 to 19.2.

Looking at the microbiologic data for this study we see again, analogous to the otitis externa studies, on a per subject basis the changes by the medical officer did not make that much of a difference.

And when we look at a per pathogen basis we see that the eradication rates are still quite high for the Ofloxacin arm, at 93 percent or better for the top five pathogens. And these five pathogens are what you would expect to see in this. You see the top three for otitis media in the usual sense, those children who have intact tympanic membranes, and you also see Staph aureus and Pseudomonas, those organisms you expect to see in subjects who have a perforated tympanic membrane.

As Dr. Seidlin pointed out, the Pseudomonas aeruginosa isolates are rather low in number in this study because subjects who had a pseudomonas isolate as their sole pathogen at baseline where to be excluded from each of the study arms in order to protect the study blind.

Looking at a clinical cure rate on a per pathogen basis we see that Ofloxacin had very good clinical cure rates for all these five pathogens and they were higher than the Augmentin™ arm except for Moraxella catarrhalis, and this was really not that much different.

And again the Pseudomonas is not really a good comparison because of the study design, and we don't really consider Augmentin™ to be a drug that

you would use for Pseudomonas.

Looking at the overall clinical and microbiological success rates in this study, again the medical officer's changes do not make much of a difference. The clinical and microbiological success rate for the Ofloxacin-treated subjects was 67 percent versus 78 percent for the Augmentin™ arm.

Looking at the adverse events in this study, overall Ofloxacin had a lower adverse event rate, and this was statistically significant. It was 42 percent of Ofloxacin subjects versus 52 percent of Augmentin™-treated subjects experiencing an adverse event.

Diarrhea accounted for much of this difference, with 29 percent of the Augmentin™-treated subjects experiencing diarrhea versus five percent in the Ofloxacin group. And rash was seen in a higher percentage of Augmentin™-treated subjects: 90 percent versus two percent in the Ofloxacin group.

As Dr. Gates described, a subset of these subjects had audiometry performed as a secondary sort of safety measure, and these subjects had to be at least four years of age or older so that they could cooperate with the test.

Standard audiogram frequencies were tested

and there was no significant change in the puratone average for bone conduction at 4,000 Hz, and in the air conduction study, Ofloxacin actually showed at an improvement compared to Augmentin™: in 68 percent of the subjects versus 35 percent of the subjects.

The second study that was done for acute otitis media in children with tympanotomy tubes -- this was protocol 007, which was a multi-center, open label study using historical and current practice control arms. Otherwise the design was similar to that in study 008.

There were a total of 600 subjects in this study; 226 of those were Ofloxacin-treated subjects and all of those subjects received at least one dose of study medication.

The data collected in this study for the Ofloxacin group was very similar in detail to that collected for protocol 008. For the historical and current practice group studies the data was collected retrospectively, and unfortunately there was no data collected on the baseline disease characteristics or the treatment regimens used for the subjects in historical and current practice groups.

The primary efficacy variable in this study was to be the success rate -- and that is dry ear, or

cure -- for the Ofloxacin-treated subjects who are deemed clinically evaluable versus the success rate -- dry ear rate -- for subjects in historical practice group who had a follow-up visit.

In this study the medical officer made essentially, no real changes to the applicant's data and the overall success rates were, for Ofloxacin in clinically evaluable population a success rate of 84 percent, versus 64 percent for the subjects in the historical practice group who had a follow-up visit.

What we can see is that the success rate in the historical practice group subjects who had a follow-up was 64 percent, and it was 70 percent with the current practice group subjects. It's notable to see that these are similar rates.

The microbiology in this study was not significantly affected -- I'm sorry, the success rate by pathogen, were very high for the Ofloxacin-treated subjects. There was not data collected on the microbiology for historical or current practice groups.

These are the top five pathogens found and they are the ones that the applicant seeks labeling for, and they are the ones you would expect to see in this clinical entity. The usual pathogens of otitis

media and Pseudomonas and Staph aureus. And the applicant's clinical cure rates for these top five pathogens were at least 83 percent.

Looking at the subjects who were both clinically and microbiologically evaluable -- and in the Ofloxacin arm this considers all baseline pathogens, not just those top five -- again, the overall success rate for that combined response -- clinically and microbiologically -- was also very high; it was 86 percent.

For the safety data study the data was collected only for the Ofloxacin-treated subjects and the findings were similar to those seen in study 008.

So what we're left with in the study of acute otitis media in children with tympanotomy tubes are two studies: one, a randomized, evaluator-blinded study with an active comparator, and an open label study with historical and current practice arms.

And looking at the data from the two studies, the question that is posed to the advisory committee is: are these data adequate to support the safety and efficacy of Ofloxacin Otic Solution for the treatment of acute otitis media in children with tympanotomy tubes?

Now we'll look at the last clinical

indication, chronic suppurative otitis media in adolescents and adults. And there was one study done for this and that was protocol 006. This was a multi-center, open label study with historical and current practice groups. And recognizing that there is no comparator agent for this we allowed the historical practice group design.

The Ofloxacin was dosed for 14 days in this study as opposed to ten in the other studies. Subjects were to be at least age 12 years and they were subjects who had purulent otorrhea with a chronic perforation of the tympanic membrane -- chronic perforation being described as a perforation of at least 21 days duration.

There were 490 subjects enrolled, of whom 207 were in the Ofloxacin arm. In this study inclusion and exclusion criteria were the same for all three arms: Ofloxacin, historical practice, and current practice groups. The information on historical and current practice groups was collected retrorespectively, and as we'll see in protocol 007, unfortunately there was no data collected on the baseline disease characteristics, or the treatment -- which regimen was used in those two arms.

Also analogous to protocol 007, the primary

efficacy variable was to be the success rate described as dry ear, or complete cessation of otorrhea. In the Ofloxacin-treated subjects who were considered clinically evaluable versus the historical practice subjects who had a follow-up visit, and we see in the study the success rate was 91 percent for Ofloxacin versus 67 percent for the historical practice group subjects who had a follow-up visit. And similar to study 007, historical practice and current practice groups had similar success rates.

The microbiology, the overall clinical/microbiological success rates for the subjects who were microbiologically and clinically evaluable were also quite high in this study. At least an 86 percent success rate for the top six pathogens, and these are the ones that the applicant seeks labeling for. And we see that the predominant pathogens were Staph aureus and Pseudomonas which we would expect; protease mirabilis also come in at a fairly high number.

And what we can see from this study is that these pathogens -- there's a shift away from the respiratory and pharyngeal pathogens that you see in the younger age groups, and these were -- the next most frequent organisms were more of an enteric

nature.

The safety results for study 006 were only collected for the Ofloxacin-treated subjects. Adverse events most frequently seen regardless of relationship to the study drug were taste perversion at 17 percent, and seen in approximately five percent of the subjects were headache -- earache, headache, and dizziness. And most of the adverse events were mile to moderate intensity.

So in summary, for the study of chronic suppurative otitis media we are left with a single, open label study. Ofloxacin showed a clinical response rate of 91 percent in the clinically evaluable population; however, the interpretation of this, comparing to historical/current practice groups success rates, is limited by the lack of data on the baseline disease characteristics and regimens used in those arms.

This leads us to the question for the advisory committee and that is: are the data sufficient to support the approval of Ofloxacin Otic Solution for the treatment of chronic suppurative otitis media in adolescents and adults?

This concludes my presentation and I'd be happy to address any questions.

CHAIRMAN CRAIG: Questions from the members? Dr. Norton.

DR. NORTON: Dr. McDonald, I wanted to ask you and perhaps the sponsor, in study 007 there's a rather large difference between the clinically evaluable success rate and the intent-to-treat. There's also a lot of people who aren't evaluable, obviously. And I wonder if you could address that, or Dr. Seidlin?

DR. McDONALD: Well, I think that's somewhat misleading to call it an intent-to-treat analysis sort of. It's the -- the applicant actually took a very conservative approach and they included in the denominator all subjects, but not taking -- actually I should say, in the numerator they only included those subjects who were considered clinically evaluable.

Where those subjects, you know, were deemed success at visit 4 but had a reason to be considered non-clinically evaluable they were not included in the numerator, they were included in the denominator. So it's not exactly an intent-to-treat analysis; it's a more conservative approach. So the success rate is a little bit lower than you might expect, compared to what it would be if it was a true intent-to-treat

analysis and compared to the clinically evaluable.

If Dr. Seidlin has a different explanation it might --

CHAIRMAN CRAIG: I assume that's what you're looking for? Or is it?

DR. SEIDLIN: As Dr. McDonald pointed out, we only considered clinically evaluable cures as cures for the intent-to-treat evaluation, rather than investigator assessed improvements at visit 4. So it was an extremely conservative intent-to-treat analysis. The slide I was looking for, in fact, had more to do with the reasons for exclusion -- and that's slide 313, Robert.

Looks a little small from here; however, I'll read it to you. The most important reason was protocol non-compliance. We also exclude from both arms any -- well, there's only one arm there -- all subjects who had a Group A Strep because there was concern that these patients might need systemic therapy. That accounted for about five percent of subjects, which is very consistent with what's been reported in the literature.

Seven percent of subjects were excluded because they took a prohibited medication. Another five percent were excluded because they developed

infection in the contralateral ear which was not infected at baseline. Another six percent for visit non-compliance.

We also excluded patients who had fungus as their sole baseline pathogen, considering that they might require a different sort of therapy.

CHAIRMAN CRAIG: While you're up there, you have no baseline data on the concurrent group that you were using to compare with your treatment arm?

DR. SEIDLIN: In the initial protocol we did not collect data on therapies that were administered. However, we have subsequently gone back to look at protocol 006 in a supplemental protocol, to see if we could ascertain treatments that were administered for subjects in the current practice arm. That data is still interim and preliminary but I'd be happy to show it to you.

CHAIRMAN CRAIG: But the FDA hasn't seen it, is that right?

DR. SEIDLIN: They have, indeed. I faxed it to them earlier this week, so they've seen it. So here are the therapies used in the current practice such as in protocol 006. First we categorize them by whether they were treated with an otic solution or a combination of an otic and an oral, or whether we had

no record of what they were given.

None of the subjects were treated with an oral alone. As you can see, 75 percent of the subjects were treated just with otic solution and 19.6 percent -- about 20 percent were treated with a combination. As you probably have noticed, this protocol was conducted both at U.S. sites and Latin American sites and this data is broken down by region here. And it really doesn't differ substantively between the U.S. and Latin America.

CHAIRMAN CRAIG: But the main thing is, we still don't know if the groups are comparable? You don't have that data, right?

DR. SEIDLIN: Comparable with regard to what?

CHAIRMAN CRAIG: Baseline characteristics. I mean, are we looking at apples and oranges or are we looking at all apples?

DR. SEIDLIN: It's problematic. All subjects enrolled in both the current practice and historical practice arms had to have mucopurulent or purulent otorrhea at the time of enrollment. That was the same criterion as was used for the prospective Ofloxacin arm. So that is really the only statement I can make about their baseline characteristics.

The fact that there was no difference in treatment response between the historical patients and the current practice patients, argues -- albeit not terribly strongly -- that there wasn't much difference, at least in response to therapy, and perhaps therefore, in the baseline characteristics between the historical and the current practice arms.

CHAIRMAN CRAIG: And do you know about any of those oral drugs? Were any of them anti-pseudomonal agents like ciprofoxasine?

DR. SEIDLIN: Would you go to the previous slide? This lists the drugs that were administered. I apologize that's not summarized a little bit better. But you can see that for all centers the most common drugs were Cortisporin™ Otic and a combination dexamethasone and neomycin.

You see that the Cortisporin™ was the U.S. drop of choice and the dexamethasone plus neomycin is the Latin American drop of choice. Another drug that was used in the United States was kind of a homemade, triple powder which includes chloromycetin, mycostatin, and boric acid, and is administered by puff into the ear. And that was used in 12 U.S. subjects.

The oral -- you can see that topical

Gentamicin was also used in the U.S., and you see oral amoxicillin was also used in these subjects -- both in the U.S. and in Latin America. So that's the data on 56 of the subjects. A total of, as you call, 63 subjects were enrolled in the current practice arm and we're trying to continue to capture the data on the rest of those subjects.

CHAIRMAN CRAIG: Any other questions? Dr. Melish.

DR. MELISH: I'm just puzzled as to why you didn't use a placebo arm with the vehicle? Not having a comparator and actually probably the ideal situation to see whether your treatment is better than nothing?

DR. SEIDLIN: There was a lot of concern about using a placebo solution because we might be flushing organisms from the external canal into the middle ear without using an antibiotic solution to sort of take care of that problem. So there actually was quite a bit of discussion about whether there could be a placebo comparator and it was rejected on that basis.

CHAIRMAN CRAIG: Why wasn't a comparative study done in the suppurative otitis media group?

DR. GIEBINK: Well here, there is no topical comparator that could have been used. As you know,

nothing is labeled. Excluding patients with Pseudomonas would have been a problem because that really is one of the two most common pathogens. We don't have in this population, the incidence of the typical acute otitis media pathogens that you see in the children with tympanotomy tubes.

CHAIRMAN CRAIG: I mean, you still did it with the tympanotomy tubes but I guess you felt that -- I mean, did the consultants say that you were going to need parenteral anti-pseudomonal agents?

DR. SEIDLIN: That was the feeling. And in fact, when we looked at, you know, this population, systemic quinolines were not being used for this indication. In fact, no systemic quinoline has an indication for treatment of otitis media. So we really were in a bind in terms of trying to find an antibiotic that even had an acute otitis media indication that would cover Pseudomonas.

CHAIRMAN CRAIG: But, I mean, at least -- maybe I'll ask our consultants that are here. I thought it was mentioned before that parenteral drugs, oftentimes anti-pseudomonal agents, are some of the things that were administered? At least Dr. Myer talked about even using home IV therapy for such infections.

DR. GRUNDFAST: Unless I misunderstood what Chuck Myer was saying, that would be a rare instance. That would be for patients that were refractory to two levels of prior treatment: first just topical agents, and second, oral antibiotics administered at home.

And patients -- and I think it's a very, very small subgroup -- that would be refractory to those prior steps in management and then would require parenteral antibiotic. That would be quinoline. I think that would be a rare instance. Is that not your -- that's not what you took away from his presentation?

CHAIRMAN CRAIG: I mean, I always -- to me I guess, it's maybe the definition. You know, you can have -- I guess chronic suppurative that I thought which was something that was going for a long prolonged period of time was a very high incidence with Pseudomonas, and that drops might not be effective if there was a higher percentage that were used.

But as I say, I may be, obviously misinformed.

DR. GRUNDFAST: That would be a very, very small set of the entire population of patients that are treated for otorrhea, and in those instances we

are very suspicious about underlying cholesteatoma or mastoiditis. It's not the kind of thing that would be I think, the indications we're talking about here.

CHAIRMAN CRAIG: I guess I -- to me, the definition is, what do you call chronic otitis media? And Dr. Myer said it needed to be going on for two months. Did all of these people have this going on for two months?

DR. SEIDLIN: The inclusion criteria for the protocol said that they had to have a perforation for three weeks. However, it turns out that the median duration of perforation was close to two years in these patients. I think it was 700 and some-odd days. So indeed, they all had chronic perforations.

Now, I have to sort of go to a backup slide for the duration of otorrhea in subjects, but my recollection is that it was -- in the U.S. subjects it tended to be more intermittent perhaps. They get treated more often and the median duration of this episode of otorrhea was ten days; whereas in the Latin American subjects the median duration of this episode was about 100 days.

So they clearly are not getting treated as regularly and as aggressively. But the perforations were of very long-standing duration.

CHAIRMAN CRAIG: Yes?

DR. McDONALD: That information on the chronicity of the otorrhea was for the Ofloxacin arm, correct? You don't have that information on the historical and the current practice controls?

DR. SEIDLIN: That's correct.

DR. McDONALD: I think a point that we should make is that, I think now the FDA has seen the data on -- some of the data you have on the current practice and historical control arms, but as of the, referring to the facts that you sent to us a couple of days ago, we haven't really had a chance to look at these agents that were used. And I think that we basically worked with the database that gave us, not a lot of information about the historical practice or current practice control.

CHAIRMAN CRAIG: Yes, Dr. Henry.

DR. HENRY: If you could just clarify, how was the microbiology data collected? How was that done in kids and adults?

DR. SEIDLIN: You're referring to the otitis media studies or to the otitis externa studies?

DR. HENRY: Well, all of the microbiology that's available. What was the technique that was used?

DR. SEIDLIN: For otitis externa the swab was inserted into the ear canal; that was the technique. The ear was not cleaned before that was done.

For the otitis media studies the canal was cleaned first and the swab was supposed to be taken from the tube after cleaning, and then was inoculated into a tube and transported to a central laboratory.

The follow-up cultures were supposed to be obtained for any subject who had otorrhea. If no otorrhea was present a culture was not to be obtained. And this is of course because this is not a sterile site and cultures obtained from non-sterile sites could yield contaminants which would be difficult to interpret.

So any subject who had otorrhea, regardless of quality -- serous purulent, mucopurulent -- was cultured.

CHAIRMAN CRAIG: Okay. Any additional questions? Could we go back then to, I guess it's slide number 24, which is the first question. And this has to deal with the data for otitis externa. As was mentioned we had two studies, one in adults and one in children. They both showed equivalent data with the comparative agent which what Cortisporin™.

And the major difference between the two studies was that the rate of efficacy was less in adults than it was in children, although in the FDA and also in the sponsor's presentations, there were some factors that appeared to be somewhat different between the two and were more common in adults that possibly could explain.

And so we're asked, are the data sufficient to support efficacy in safety of FLOXIN™ Otic in the treatment of adults with otitis media?

We have our consultants here, Dr. Wald and Dr. Grundfast, and I guess I would ask first of all from their point of view, what they thought of the data.

DR. WALD: I think the data looked very impressive and I think it will be wonderful to have this kind of a drug available to us.

CHAIRMAN CRAIG: And it's your experience and practice that adults frequently don't respond as much, possibly in diabetes or things like that, as well as children?

DR. WALD: Yes, I think for adults the issue may be less important. I think the principal problem with Cortisporin™ is local discomfort, and the results look pretty comparable for that particular

group. For children, again, I think the comfort issue will be important.

CHAIRMAN CRAIG: Dr. Grundfast, any additional comments?

DR. GRUNDFAST: I was impressed by the data. I just had a question -- I'm not sure who can answer it. In all these years of using Cortisporin™ which has neomycin and hydrocortisone, and also the other agents -- Tobradex™ which contains dexamethasone -- we always thought that the steroid was doing something. It's not doing anything?

CHAIRMAN CRAIG: Maybe not. Okay. Any comments from any of the members? Well, we see none. Let's take a vote.

So all that think that the data are sufficient to support it, raise your hands. I see it being unanimous.

That's for adults. How about the next question for children? All that think that it's -- in favor, raise your hand. Again, it's unanimous.

Could we go on then to the next question which is slide 39. Question number 2 is for acute otitis media in children with tympanotomy tubes. We have two studies. One of these is a comparative study with Augmentin™ in which the drug did prove to be

similar.

I might remind you that this is not an entity that we've given approval for before, so we don't have any approved agent. But the agent that was used is an agent that is approved for otitis media.

The second study was one which was done along with a retrospective control group for which again, we really don't have all the data to be sure that the groups are comparable, and also what drugs that they all received.

So in essence the second study is really a single drug study with the compound, not a comparative study. But the results of that study were very similar to what had been obtained in the comparable study.

So again, I'll see if there's anybody that wants to make any comments. Are you all satisfied with the -- I guess our consultants -- with the comparative agents, since this is not a disease that the FDA has given approval to? Is amoxicillin/clavulanate -- was that an appropriate agent to use or should there have been something different because of the Pseudomonas problem?

DR. WALD: I think in an acute onset of otorrhea in a child who has indwelling tubes it's

commonplace to have one of the, you know, usual antimicrobial agents that you would use for acute otitis media. So I think in that sense Augmentin™ was a reasonable choice.

And I think while these results are unexpected I wouldn't have anticipated that a topical agent would have worked so well. I think the results were clear.

CHAIRMAN CRAIG: Dr. Grundfast.

DR. GRUNDFAST: There has, for the information of all those present, there has always been a dichotomy in the beliefs of pediatricians versus otolaryngologists about treatment of otorrhea, especially with tympanotomy tubes. And I think Dr. Wald expressed surprise but no otolaryngologist would be at all surprised.

As Dr. Myer said this morning -- or this afternoon -- otolaryngologists virtually never treat otorrhea with tympanotomy tubes with a systemic agent, and are always a little bit chagrined that their pediatric colleagues seem to feel the necessity to treat with systemic agents.

So the data wasn't surprising to otolaryngologists I think.

CHAIRMAN CRAIG: What might you have used as

a control if you were going to --

DR. GRUNDFAST: It wouldn't have mattered because we never felt that the systemic agent was of any importance, so Augmentin™ was fine. I think that's probably what's out there, but --

DR. MELISH: So would you have used Cortisporin™?

DR. GRUNDFAST: That's what's being used; that's the current practice for otorrhea with tympanotomy tubes. And I did have -- in regard to this, I wasn't sure if I missed it, but in the evaluation when these topical agents -- specifically the Cortisporin™ is prescribed for children with otorrhea with tympanotomy tubes -- not infrequently a parent will say that they had to stop giving it because the child couldn't tolerate it because of pain, or discomfort, or crying. If it's used in an infant they can't express pain but they scream.

Was that addressed? Were there any times in which it had to be stopped for that reason? Or did I miss that part of the presentation?

CHAIRMAN CRAIG: The question was on pain and stopping therapy.

DR. SEIDLIN: That's slide 302. Now remember, we did not use Cortisporin™ in this

protocol. We did not have --

CHAIRMAN CRAIG: Are you still looking? Is that --

DR. DOHAR: While she's looking I just want to point out to Kenny that the pHs of the two agents are very different. Cortisporin™ as you know, are down in the twos and threes. The pH of this agent is almost neutral.

DR. GRUNDFAST: Okay, so it was perhaps the pH that caused the pain? Okay.

DR. SEIDLIN: The bottom line is, we didn't have any withdrawals from the Ofloxacin arm because of the pain. There were application-type reactions in otitis externa with Cortisporin™ and they slightly exceeded those with Ofloxacin, but I wouldn't make a big deal out of it.

Remember, any subject who had a problem of course, one would be unlikely to enroll in our trial where they might get randomized to Cortisporin™. So I think we may have lost the ability to make that comparison.

In any event, here you see the list of adverse events that caused discontinuation from treatment in protocol 008, and earache is zero in the Ofloxacin arm.

DR. GRUNDFAST: Mr. Chairman, I have one more question if I may?

CHAIRMAN CRAIG: Yes. Go ahead.

DR. GRUNDFAST: I'm not sure how the panel would consider this, but I do think it needs to be considered. I think the figure was given that 750,000 children in the United States each year receive tympanotomy tubes. It's one of the most common operations done in children.

And it's common practice at the time of the surgery to instill otic drops in the ear, for reasons that are not exactly clear, but it is common practice. So I'm wondering how the panel would deal with labeling and concerns about the cost, and in bringing up the cost I'm wondering about the comparison cost for this agent for this indication versus the cost now for Cortisporin™, Tobradex™, the ophthalmic sulfa drops that are being used?

Because I can see a significant financial impact if each child were to receive drops in the ear at the time of -- if each of the 750,000 children to receive in the operating room, these drops because it's now approved for use with tympanotomy tubes, go home with these drops and then if managed care corporations had to pay for this, if the government

had to pay for this, I was wondering about how we would deal with that?

CHAIRMAN CRAIG: I'm not sure that that is something -- at least what it sounded like from before is, there seems to be -- at least I heard was more of a need for something out there that's not potentially ototoxic. But I guess you're saying that many of the things that are currently used are really not that ototoxic and they're considerably cheaper. And what we may be doing is markedly increasing the cost of overall therapy. Am I right?

DR. GRUNDFAST: I think you -- yes, I'm just raising -- yes. And it's the issue that's been raised and I don't know whether it's something you would deal with in labeling or -- I don't know how to --

CHAIRMAN CRAIG: So you would have been happier if they also had a control arm here with using a topical agent?

DR. GRUNDFAST: Absolutely for those 750,000 children in the perioperative period. Absolutely. I think saline probably would be equally effective, so I'm concerned about this becoming the common practice now to use these drops instead of Cortisporin™, Tobradex™, or whatever -- sulfa, ophthalmic vasocytin is commonly used in the operating rooms now. So I'm

just a little concerned about that.

CHAIRMAN CRAIG: When I looked at the numbers, I mean, outside for the staff, looking at Pseudomonas it only made up about ten percent of the organism, so it's not a -- didn't look like it was a very big player in this particular disease. But Staph aureus was a fairly big player with, I guess, 28 and 25 in the two groups.

But clearly, the biggest numbers were still Haemophilus and pneumococci. Does anyone know of any data with the other topical agents, that has looked in this entity with tympanotomy tubes to see if it's active at all against those organisms? Nobody's aware of anything? Dr. Reller? Oh, wait.

DR. PARSONNET: I just think the point being made is slightly different, which is that there's no -- what's being suggested is that people use this prophylactically, we use eardrops prophylactically -- and do we want to put something in the labeling saying that this has not been approved for prophylactic use in the period?

CHAIRMAN CRAIG: Oh, okay. Thank you very much. Yes?

DR. CHIKAMI: What in fact, the applicant has requested are indications for therapeutic use, and

if the committee feels that the data support those indications, that in fact, is the indication that would be granted in the product labeling.

CHAIRMAN CRAIG: I didn't get that you were talking about prophylactic use. Dr. Reller.

DR. RELLER: Is there any labeling in what is used that would support the perioperative prophylactic or therapeutic use of the drops? I mean, I'm struck by the distribution of organisms in this study, and theoretically, the topical agents used currently for most of these, as far as I know, have no activity. I mean, no intrinsic activity.

DR. GRUNDFAST: Is bacitracin in there? What's in --

DR. RELLER: I thought it was neomycin and polymyxin. And not bacitracin.

DR. GRUNDFAST: It's not a triple, okay.

DR. RELLER: Because I mean, for those agents, I mean, one can use them as a selective medium for the isolation of pneumococci. I mean, this is -- I mean, it points out, maybe the patients seen by the otolaryngologist and the pediatricians are different, and it gets to the fundamental pathophysiology about whether it's from the outside or the inside.

I mean, the pathogens here, the predominant

ones with the tympanotomy tubes are the interflora, so to speak, that one would have with the tubes. Sort of the same pathophysiology of acute otitis media --

DR. GRUNDFAST: Two-thirds, two-thirds.

DR. RELLER: With a blocked tympanotomy tube so that you'd basically be backed as if you had a intact tympanic membrane. In contrast to the way the drops appear to be used in otolaryngology practice as if it were an external pathophysiology with colonization and then inflammation associated with Pseudomonas aeruginosa, predominantly.

But these are interflora and not outerflora.

CHAIRMAN CRAIG: Yes.

DR. SEIDLIN: Can I make a comment on that? One of the issues I think, in using topical therapy like Cortisporin™ is, remember you're putting very high concentrations of these drugs right at the site of infection. So that the MICs that we're accustomed to thinking about are based on levels achievable with systemic therapy -- blood levels.

But in fact, when you're putting these solutions in the ear you're putting in milligrams per ml, which may be many multiples of the MIC that's achievable with systemic administration. So that even an agent which might not be considered efficacious,

when administered systemically for some of these organisms really ends up being, you know, so highly concentrated that it will work for these bugs when administered topically.

DR. GRUNDFAST: If I can address your concern? And I know the hour's late but I do want to explain our view so that it doesn't appear that otolaryngologists haven't thought about this.

(Laughter.)

We have thought about this and here's our view. Otorrhea is extremely common -- I think we said about 30 percent of children with tympanotomy tubes have it some point during the time that the tubes are indwelling the ear -- otorrhea in one or both ears.

Our view of that otorrhea is that it may have started as an otitis media but since you now have a drain in the ear, before you have a tube in, if you have otitis media it's behind an intact eardrum and in order to recover the organisms that you quote as the organisms that cause otitis media, you have to do a tympanocentesis as was described this morning. Then you recover those organisms and you grow them.

When you have a tube in place and you have otitis media, often it was preceded by an upper respiratory infection, it may have been caused by the

organisms that you would find when do a tympanocentesis. However, once you have drainage of liquid into the ear canal, otolaryngologists believe that liquid in the ear canal is a culture medium for Pseudomonas.

So you have a timed difference so that the -- whatever caused the initial episode of otitis media and was accompanied by a fever and an upper respiratory infection, indeed might be the three organisms which we commonly see as cultured from otitis media.

But by the time you have yellow liquid coming out of the ear, that's become a combined problem of a past, recent past otitis media with organisms that you think might be treated with a systemic antibiotic, and the current problem is the liquid in the ear canal and most likely due to Pseudomonas or other similar -- or, Staph aureus and Pseudomonas.

So we think that the otitis media was in the past and when we see the otorrhea we think of it as a combined, middle ear, external ear problem, which we think is easily treated by topical agents.

DR. RELLER: As a standard of practice, do you ever bother getting cultures in those patients?

DR. GRUNDFAST: Honestly?

DR. RELLER: Yes.

DR. GRUNDFAST: Honestly, no. Because it's always Pseudomonas, and otolaryngologists taking a swab of the ear canal and sending it off -- we learn early in our careers that it's never anything else, so we don't culture it.

Also, we try to dissuade neighboring pediatricians from culturing it because what happens is they get stuck with the Pseudomonas culture and then they start talking about hospitalization, parenteral antibiotics, and we don't -- we think it's usually not necessary. These are generally pretty healthy children who are not particularly sick, even though you've recovered Pseudomonas from the ear canal.

CHAIRMAN CRAIG: Dr. Wald, any --

DR. WALD: I was going to say, the earlier you culture them the more likely you are to recover S. pneumoniae, Haemophilus, or Moraxella; hence these cultures. And the longer you wait the more likely you are to have a predominance of Pseudomonas and Staph.

So I think it's the timing, and I think in this study they were allowed to have their drainage up to three weeks, and that's what may account for the

display. But in the very early cases, I mean, I regard it as acute otitis media and that's why, again, I would think about a systemic agent for treatment. And why I was surprised, but glad that it worked.

CHAIRMAN CRAIG: Okay. Any further comments/discussion? Well, I think we should take a vote on this question, question number 2. Are the data presented in studies 007 and 008 adequate to support the safety and efficacy of FLOXIN™ Otic in the treatment of children with acute otitis media with tympanotomy tubes?

All those in favor raise their hands. Again, it looks unanimous.

We have number 46. This is the one for chronic suppurative otitis media, in which we have one study. It's an uncontrolled trial in which we also do not have data on the baseline characteristics of the individuals and fully all the data on which antibiotic they receive.

But again, this is an indication in which there is no prior approvals for other agents, so no specific previous approvals that one could use for comparable agent.

And the question is: is the type of data where one looks at 50 potential different regimens the

kind of comparable data that one would be satisfied with for approving for this indication?

I guess I'd ask first of all, from our experts from the ENT field, are they concerned on the lack of comparative agent and should this have been a placebo-controlled trial, or if not a placebo could they have come up with a comparative agent that could have been used?

DR. WALD: I think a placebo trial would be difficult here because, I mean -- and again, as you said earlier, to qualify you have to have pretty persistent drainage, so in a sense, you have either failed to respond to something or you had no treatment and you've not gotten better spontaneously. So I don't think that would be legitimate.

And I think, as Dr. Grundfast said before, I think it's very common in the community to try ototopical therapy first for the child who's been draining transiently. And usually kids who come to hold a diagnosis of chronic suppurative otitis media have by definition, failed those therapies which permits them to have a duration of otorrhea which would qualify them for this study.

So in some sense I think there isn't really a comparable control in those cases that do fail

ototopical, they do go on to parenteral therapy as you said before. What Dr. Grundfast was saying, that's unusual -- we probably still do it 12/15 times a year. But it's not very common that children fail that treatment.

CHAIRMAN CRAIG: But do we know that these patients failed -- I mean, why didn't they use Cortisporin™ in this particular study? As a comparative agent.

DR. WALD: I presume that there have been some earlier therapies.

CHAIRMAN CRAIG: I mean, the problem is I think is we don't have that information. We don't know. Dr. Parsonnet.

DR. PARSONNET: I have a question, basically for statistical things. If they had had a -- if they had a 91 percent success rate with this, which is a really excellent success rate -- had they had a comparator arm, is it at all likely that they would have found that this was significantly worse than that comparator arm? What would the success rate have had to have been for them to say that this is an inferior thing to use?

DR. SEIDLIN: I just wanted to address the point of not using Cortisporin™. Remember,

Cortisporin™ carries a warning in its label for caution in use with patients who have a non-intact tympanic membrane. Certainly under those circumstances we could not use it as a comparative agent.

DR. WALD: Had these patients though, many of them received therapy prior to entering the study?

DR. SEIDLIN: In talking to a lot of the investigators, these patients have had this problem for years, and most of them have received therapy in the past; many of them had received Cortisporin™, neomycin, and so on in the past. So indeed, many of them had received that therapy, but we didn't feel that in the context of the clinical trial we could use that.

CHAIRMAN CRAIG: Do we have any longer follow-up to these patients to see if they're now draining again?

DR. SEIDLIN: Only anecdotal. I've actually been told that some patients have -- it's important to dry up the ear. Many ENTs feel it's important to dry out the ear before they can go on and do a tympanoplasty. And we've had anecdotal reports that there were subjects who couldn't be dried up before who have now gone on to tympanoplasty, but that's

purely anecdotal.

CHAIRMAN CRAIG: Dr. Reller.

DR. CHIKAMI: Can I --

CHAIRMAN CRAIG: Oh, sure.

DR. CHIKAMI: I just wanted to make a couple of brief clarifications. In regard to the use of a historical control group, there are clearly situations where we accept data from historical control designs. Those situations in fact, where there are few patients to study, where there are no approved therapies, or in fact, where you're sending a patient populations which have failed all approved therapies and it would be felt to be unethical to randomize subjects to a non-treatment control arm.

In those situations, however, we think that, as in any historical control comparison, there are important design issues in terms of collecting important baseline information, information on response and other factors which might affect the observed response rates in the historical control group as you compared them to the prospectively followed control group.

To address Dr. Parsonnet's question, in fact if you look at the clinically evaluable subjects in that study, that the response rate was quite high.

And in fact, I mean, I'd have to crunch some numbers to find out what size or what response you would need to determine whether or not it was statistically equivalent to a theoretical response, say, of 95 percent. But in fact, you're right; that's quite a higher observed response rate in that treatment arm.

And some of the inference that one might draw in making historical comparison is, what you expect the response rate to be in a previously followed treatment group.

CHAIRMAN CRAIG: And the concern though, could be that you're dealing with a much milder group than what was seen with the results that tended to give a lower result.

DR. CHIKAMI: And I guess the issue is that with the lack of information we don't know, in fact, how comparable those two groups are.

CHAIRMAN CRAIG: Dr. Reller.

DR. RELLER: When I looked at the microbiology of study 006, it seemed to me to support the chronicity of these patients. And then taking that with the endpoint of the proportion who achieved a dry ear, I wanted to ask Dr. Grundfast, with patients like this, if one could achieve a period of a dry ear, are these persons who might shift the

category of being candidates for tympanoplasty?

DR. GRUNDFAST: Yes.

DR. RELLER: I mean, is that what you're trying to achieve?

DR. GRUNDFAST: Yes, yes.

DR. RELLER: Or put another way, with persons who, for whatever reason, have persistent wet ear with a chronic perforation, does that prevent reconstruction of the eardrum, in and of itself?

DR. GRUNDFAST: It doesn't entirely prevent it but it makes the successful outcome of the tympanoplasty less statistically likely. So that we feel that if we operate on an ear that doesn't have endemitis mucosa, or liquid in it at the time and significant inflammation, that the result of the tympanoplasty would be more likely to be successful.

The only thing that -- I'm sorry, did you have another --

DR. RELLER: No, no.

DR. GRUNDFAST: I was wondering if Dr. Seidlin -- I hope I pronounced it correctly -- could you just restate the comment you made a few moments ago about intermittent versus persistent? Because it's extremely important here.

To an otolaryngologist persistent otorrhea

is much more likely to be associated with, yet to be diagnosed -- cholesteatoma or some other serious condition that's yet to be diagnosed -- versus intermittent otorrhea with a perforation, which in children often is a result of swimming in the summertime, or some entrance of bacteria from the external environment into the middle ear.

And you mentioned that. But I wasn't sure -- you had a length of time but I wasn't sure that whether during that length of time your study subjects actually had had persistent otorrhea versus intermittent otorrhea.

DR. SEIDLIN: They obviously have to have otorrhea at the time of enrollment, and the median duration as I said, in the U.S. just in that episode before enrollment was ten days; in Latin America it was much longer. The vast majority -- it may be all of the subjects treated in this protocol, were treated by ENTs.

The presence of a cholesteatoma or any surgery in the treated ear in the previous year was an exclusion criteria. So we were trying to eliminate any patients who might have cholesteatomas, and as far as we know, we didn't have any subjects who failed to meet that criteria.

So I think we did effectively get rid of patients with cholesteatoma, and I think we do have a mix of patients who had intermittent and persistent drainage in this study, but I don't think we had any with cholesteatoma or other tumors in the ear.

DR. GRUNDFAST: Now Mr. Chairman, to bring this point to closure then, I'm not informed on the FDA procedures but will the requirements for labeling, should this be approved, indicate that after a certain period of time if otorrhea persists, that other diagnoses should be considered? Or will it have a time limit on use in otorrhea? Is that something that you ordinarily do?

CHAIRMAN CRAIG: I think without the data they would have trouble -- well, go head. I'll let the FDA start.

DR. CHIKAMI: There are in fact, certain cautionary or precautions that are included in labels for all pharmaceutical products, and if there are issues that relate to safe use of a drug such as ruling out other confounding conditions or advice to physicians that, if a condition persists that other conditions should be ruled out -- for example in this case, cholesteatoma -- those sorts of statements may be added to the product labeling.

CHAIRMAN CRAIG: Yes?

DR. DOHAR: My name is Joe Dohar. I'm a pediatric otolaryngologist at Children's. I just want to make two points of clarification. The one issue was the absence of a placebo in this trial, in the form of a topical placebo.

And Dr. Seidlin had pointed out there was a concern about flushing organisms into the ear from the external canal, and I think the other issue that most otolaryngologists believe is that part of the disease process here and the pathophysiology, involves the perpetuation of a moist, a wet environment in the ear.

The other concern that other people have is fungal overgrowth which will perpetuate the otorrhea. So I think that most people that were consulted felt uncomfortable recommending a sham, and felt that it would be problem with the human rights committees at the institutions.

The only other comment I wanted to make, just as a point of clarification is, that I hear some comments that might be confusing this chronic suppurative otitis media, because people are assuming that the word chronic is relating to the duration of the drainage.

And I think that the defining criteria here

for this diagnosis is the fact that there's a chronic perforation that's present that intermittently drains. The timing for the drainage however, doesn't define that. And I just wanted to be sure that was clear.

DR. WALD: I don't think that's so clear. I mean, I think the majority -- I mean, I think even what Kenny was saying, I mean, if the patient drains for five days you don't think -- and it stops spontaneously, you don't think about it in the same way as if he drains for 28 days. So I think the duration of the drainage in fact, is pertinent, as well as the duration of the perforation.

DR. DOHAR: I think you're right. I think that if you look at the definitions in our textbooks on how this disease is classified -- if you look under the standard definition of chronic otitis media -- there's chronic otitis media inactive, which basically refers to an ear that has a chronic perf that is dry at the time you're looking, and chronic otitis media active means that you've got a chronic perf that is draining.

And I think that's what this indication speaks to. I think you're right, Ellen, that the difference -- certainly an ear draining for 30 days is a different ear than an ear draining in ten days. But

the defining feature here is the chronic perforation and not the length of the drainage, in terms of how the protocol was designed.

CHAIRMAN CRAIG: Dr. Azimi.

DR. AZIMI: Just a point to ask. We were told that these people had drainage for a long period of time before treatment here. Were they followed for a long period of time after the 14 days of treatment to see if they actually recur?

DR. SEIDLIN: There was no long-term follow-up built into this study. I've just put up a slide -- which you can't see because it's behind you -- showing the mean and median duration of drainage in this trial. And you can see that the mean was 97/98 days, with a median of 28. So most of them had had pretty persistent drainage.

Some of them had had shorter duration of drainage. We did not have a long-term follow-up built into this study. On the other hand, there's really no reason to believe that a short course of therapy which eradicates infection once, would prevent reinfection.

DR. AZIMI: But you didn't follow -- the last drop was given and the patient was not seen at all, or --

DR. SEIDLIN: Oh, no --

DR. AZIMI: You saw the patient --

DR. SEIDLIN: The patient was seen -

DR. AZIMI: -- and the ear was dry and you didn't get any more cultures but do we know five days later whether the same organism was present, the same individual with some drainage, maybe?

DR. SEIDLIN: The way this was designed was, the patients got 14 days of therapy and then the test-of-cure visit was seven to ten days later. So they had to have a dry ear at the visit right after completion of therapy, and seven to ten days later in order to be considered cured.

DR. GRUNDFAST: And no subsequent follow-up over a year?

DR. SEIDLIN: No, there was not any follow-up beyond that test-of-cure visit.

CHAIRMAN CRAIG: Dr. Reller.

DR. RELLER: Dr. Grundfast, with a persistent perforation, if there's a response to, for example, this compound and the ear remains dry, can one assume that there is no complicating, underlying problem -- cholesteatoma, etc. -- for practical purposes?

DR. GRUNDFAST: In general, yes. And then -- the cautionary note that I would like to see in

labeling related to your question is that if the drainage recurs or persists for a length of time greater than three weeks, that there could be a serious, underling ear condition.

But the answer to your question was in the short-term, we consider it no underlying problem, but we often then see those patients two months later, four months later, six months later, and if it's over a 3- or 4-year period this particular problem has recurred four or five times, we would go on to a CT scan looking for some underlying problem.

DR. RELLER: And if the ear remains dry, do the chronic -- the previously persistent perforations, do they heal on their own or do they need tympanoplasty?

DR. GRUNDFAST: It depends on the size and location of the perforation and the condition of the intact, remaining portion of the eardrum. It depends; not necessarily.

DR. RELLER: And when, either owing to that sort of time guidelines, when should a patient go to you? That is, if there for example, would be therapy and there were persistent drainage or recurrent drainage, in the context of a persistent perforation, when does one need not to just have otic solution put

in more, but sent to you? Or to one of your colleagues?

DR. GRUNDFAST: Yes, I would say it would be a matter of weeks. If it hadn't cleared within say, two weeks, I think that patient should be referred for further evaluation.

DR. RELLER: I ask these questions because it seems to me that, you know, given the context in which this is considered, that these considerations are important for putting some boundaries around a first, approved agent. If that's the way it turns out.

CHAIRMAN CRAIG: Dr. Melish.

DR. MELISH: I'm still concerned about the historical and current practice control. No significant difference between the two of them but two-thirds of those patients improved, I guess, at some period after seeing an otolaryngologist and having one of these multiple interventions or no intervention.

So it is clear that there's a statistical difference and that 91 percent sounds awfully good for the clearance of a, you know, of an ear that's been abnormal for such a long period of time. But I'm concerned that, you know, this is not 10 percent or 20

percent; there is a -- if the groups are not comparable there is a cure rate with either current therapy or a spontaneous cure within the timeframe of this study.

CHAIRMAN CRAIG: What would you have done for a control? Or what would you have --

DR. MELISH: Well, if Cortisporin™ is widely used, even though it's against the label, I wouldn't have seen why not, or else maybe a systemic. I mean, I'm not putting this into an adolescent. You see them -- maybe you know they've been perforated for a long time but maybe you don't. You just know that they drain sometimes and they sometimes don't. Should they have a systemic -- either a systemic or another topical?

CHAIRMAN CRAIG: And based on the --

DR. MELISH: I don't know how I'm going to vote yet, but this is something that bothers me because I just don't see that we know this is as good as it sounds.

CHAIRMAN CRAIG: Dr. Parsonnet.

DR. PARSONNET: I have another question with Dr. Grundfast. If you had a patient that you treated with whatever therapy you had and achieved a dry ear, and then two to three weeks later, a month later, you

have drainage again. What is the usual feeling about that? Is that thought to be ineffective therapy from the first time, or is that just so common that people get reinfected and reinfected from anatomical abnormalities?

So the question is one that's been raised by a number of people is, is seeing them ten days later sufficient to say that this drug is effective?

DR. GRUNDFAST: It's probably effective in the biologic and antimicrobial category. On the other hand, the problem of recurring otorrhea is multifactorial. It to some extent, is related to personal hygiene, so that children -- and maybe even some adolescents -- who have a perforated eardrum who are very meticulous about the care of their external ear and prevention of getting water in the ear from swimming pools and other -- even just showers and so on -- would be less likely to develop second, third, and recurring episodes.

Where another child who had various other hygienic factors that were not optimum, would tend to have recurrence. So I think, we get an impression after the second or third time and we try and figure out of there was any antecedent factor that might be related to the cause of the otorrhea.

And the less we can identify an antecedent factor that's related to hygiene or upper respiratory infections -- for example, a young child who's getting recurring otorrhea, each time associated with an upper respiratory infection, we're not particularly concerned about that.

But if we see the same number of episodes of otorrhea in a child who never has any prior history of upper respiratory infections within one or two days preceding the otorrhea, we become more concerned.

Does that help?

DR. PARSONNET: Yes. So basically you think that achieving a dry ear is a microbiologic cure and the recurrences are not because you haven't eradicated the infection; it's because they're going swimming every day?

DR. GRUNDFAST: Yes, I would say -- yes. I would say the recurrences start to fall into two categories: either related to personal hygiene and some entrance of bacteria, or as I said before, a yet to be diagnosed other disorder -- most likely cholesteatoma.

CHAIRMAN CRAIG: What percentage of the cases do you usually find an organism?

DR. WALD: Almost all of them. So there --

CHAIRMAN CRAIG: So in this particular group where -- I mean, I guess you only found it in about 60 percent that you got an organism?

DR. SEIDLIN: We found a pathogen in about 60 percent. We got a pathogen that we defined as a pathogen, in about 60 percent. We did not consider such things as Staph epidermdemas, differoids, carrote bacterium, you know, other organisms that were growing and just one-plus. We discarded them as just non-pathogens. So if we considered all organisms that we cultured it would be somewhat higher.

DR. AZIMI: If you have a -- how do you differentiate relapse from recurrences of infection. If the otorrhea comes back with the same organism within a few days after the termination of therapy, then how do we know that our treatment didn't eradicate this, if it's the same organism? I mean, it seems to me like it's very difficult to know the differences between relapses and new infections.

DR. WALD: I think what Kenny said before is very important and that is, if it's you or I and there's no reason that the child shouldn't have otorrhea every time they have a new cold. And so you would understand that in that context and expect it to respond very promptly again.

I think it's in the absence of either an environmental exposure or an upper respiratory infection when you start to see otorrhea again, that you get concerned that there's either an underlying osteitis, or a cholesteatoma. And then you're really worried that there's a chronic mastoid and that once you -- every time you lift the antimicrobial therapy you're just unmasking it, and that's the time when you start to do more.

You know, you do a CT scan, you do an exploratory operation.

CHAIRMAN CRAIG: Yes, go head.

DR. DOHAR: I would just like to comment on the issue you had raised about possibly using Cortisporin™ as a comparator in this trial I think is an excellent question. And although you've heard several times today that our concern about ototoxicity for topical aminoglycosides is relatively low, I think where we are most concerned -- and if you look at the literature on the cases that have been presented where people assume that ototoxicity to topical meds was the issues -- it's in this population of patients.

Mike Paparella from Minnesota published a very good article which basically showed that patients who had chronic suppurative otitis media with perfs

that drains intermittently, in those patients who are treated with topical aminoglycosides there was a much higher degree of hearing loss than in those who were not.

And so I think the two issues of number one, not having an agent that does have an FDA label, coupled with the fact that this is probably the highest risk population of patients that would have an effect from the use of that agent, is why the study was done without a comparator.

CHAIRMAN CRAIG: Of course, why not an oral fluoroquinolone? Based on the organisms there it would look like that would be a good choice.

DR. WALD: They're not approved for use in children. If you remember from yesterday.

CHAIRMAN CRAIG: Right. Very good.

DR. RELLER: How long do you ordinarily want to have a dry ear in a patient with a chronic perforation of the drum, before considering repairing it?

DR. GRUNDFAST: Probably about a minimum of three to four weeks. You know, it becomes a matter of surgical scheduling, if you --

DR. RELLER: Oh, sure --

DR. GRUNDFAST: You want to have a dry --

DR. RELLER: But that sort of timeframe?

DR. GRUNDFAST: Dry long enough to get them to the operating room.

DR. RELLER: It may have been -- and probably was presented but I don't remember -- what was the -- when the 91 percent clinical evaluable -- the dry ears in these patients, how long did they stay dry? Did we hear that?

DR. GRUNDFAST: I think we asked that. That's a little bit of a --

DR. RELLER: In this study.

DR. GRUNDFAST: That's a lack of information that I'm curious about, but I don't think we have it.

DR. SEIDLIN: Well, they had to be dry for at least seven to days after completion of therapy. Now, some of them were dry before the completion of therapy except for the drops. But we did not examine them beyond that 10-day, post-therapy endpoint.

CHAIRMAN CRAIG: Dr. Parsonnet.

DR. PARSONNET: One last question. How were the cure rates comparable in the ones in whom you had a pathogen and the ones in whom you didn't find a pathogen? Because the question has been raised, maybe this people had very mild disease and the reason you get a cure is because they weren't really that bad to

begin with. So in the ones who had real clear pathogens and non-pathogens?

DR. SEIDLIN: Let me pull out for you the cure rate --

CHAIRMAN CRAIG: You can also look at the back of the FDA presentation, too.

DR. PARSONNET: But I don't think that says the non-pathogens --

CHAIRMAN CRAIG: Back page.

DR. PARSONNET: But I don't think that has without pathogens. I think that just has pathogens.

DR. SEIDLIN: I can't give you the ones for the clinically evaluable who were not microbiologically evaluable; however, I can show you the rates for the microbiologically evaluable. That's the best I can do at the moment, but you certainly could go back and get it.

CHAIRMAN CRAIG: Yes, those correspond to the same ones because they had the date on them. Number 60 in the book you gave us, are the organisms.

DR. SEIDLIN: I'm sorry, I have that result by pathogen but I don't have it -- the overall clinical.

CHAIRMAN CRAIG: Can I ask the FDA person -- slide number 43, isn't that the clinical response and

micro response in the high organism?

DR. PARSONNET: I was curious about the cure rate -- the clinical cure rate in ones in whom a pathogen was not identified.

CHAIRMAN CRAIG: Oh, that was not identified.

DR. PARSONNET: It's not that important because -- these cure rates look so good; I'm not sure it's that important.

CHAIRMAN CRAIG: Yes, I don't think it will be much different. Maybe a little higher. Again, I guess we're asking on this on adults and adolescents. Were a large number of these patients adults?

DR. SEIDLIN: The median age was, I believe, around 49, so that most of them were older.

CHAIRMAN CRAIG: So that a fluoroquinolone could have been used.

DR. SEIDLIN: Chronic perforations in the United States are primarily disease of older people, so that one needs to keep that in mind. That's certainly not true in the third world where chronic suppurative otitis media is a big problem in children. So I think that's a real difference between the United States and the rest of the world.

So this was primarily a study of adults. I

should say that again, Latin American subjects were younger with a median age of 35, but again, still those were mostly adults and not adolescents. So we did have a few adolescents but this was basically an adult trial.

I don't have a slide of this for which I apologize, but the cure rate in the microbiologically evaluable Ofloxacin-treated subjects was 94 percent. So I think that that argues that cure rates were quite parallel for the clinically evaluable and the microbiologically evaluable. But we certainly could break that out.

CHAIRMAN CRAIG: Any further discussion? So I guess we're coming to a vote then. Are the data from study 006, an uncontrolled trial, adequate support to safety and efficacy of Ofloxacin Otic in the treatment in adults and adolescents with CSOM?

All those in favor raise their hands. Those opposed? One? And again, my reason is that I would have -- we're starting a precedent here and I'm concerned about not having a comparative trial and I can't find a good reason why there shouldn't have been a comparative trial. And so that's why I voted no.

And what additional study would I do for my no, would be to do the study -- a comparative trial.

(Laughter.)

So are there any other questions or concerns? Yes, Dr. Melish.

DR. MELISH: It still might be worthwhile. We also don't know how long this is going to last. I mean, I think, you know, I changed my mind and voted because it was so effective in the tympanotomy tube that I thought these were analogous situations. But I was also uncomfortable about this. We don't know the persistence, either. This does seem to be the best topical.

CHAIRMAN CRAIG: Are there any other questions, or --

DR. CHIKAMI: I don't think we have any other questions.

CHAIRMAN CRAIG: Okay. Oh, Dr. Reller.

DR. RELLER: In some of the past questions there was recommendations for phase 4 studies.

DR. CHIKAMI: Certainly if the committee has recommendations for phase 4 studies we would be interested in those.

DR. RELLER: That was not part of this package; that it could be.

DR. CHIKAMI: Certainly.

DR. RELLER: I would like to see some

mechanism for following these patients up longer than ten days. Because to me, the critical issue is whether you've got the potential compounds that could dry an ear up longer to fix the underlying problem that puts them at risk for external pathogenesis, that seems to be the primary pathogens that were isolated in this study.

And that would be a very, you know, important thing to demonstrate. Plus, you know, somewhere in the labeling as was discussed earlier, you know, if you had the longer follow-up and the drug were effective in the uncomplicated or those that simply had a perforation, of achieving a dry ear for that longer period of time and then you didn't achieve a dry ear with that longer follow-up, that one would have some better boundaries in which to look for other things.

CHAIRMAN CRAIG: Okay. Any other suggestions from anybody else? Okay, that's the end of the day. Again, I would like to thank our consultants for their help for the committee, and all the committee members for hanging and staying in it for the long day. Tomorrow we're supposed to be done however, by two.

(Whereupon, the 62nd Meeting of the Anti-

Infective Drugs Advisory Committee adjourned at 5:38 p.m.)