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ATDEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ANTI-INFECTIVE DRUGS ADVISORY COMMITTEE MEETING

OPEN SESSION

Wednesday, October 29, 2003

8:30 a.m.

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Two Montgomery Village Avenue
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P R O C E E D I N G S

Call to Order

DR. LEGGETT: I would like to get started if we could. Today is October 29th. We are going to be discussing Clinical Trial Design in Acute Bacterial Sinusitis.

We will first have the introduction of the Committee.

Introduction of the Committee

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

DR. COX: Ed Cox, Deputy Director, Office of Drug Evaluation IV.

DR. POWERS: John Powers, Lead Medical Officer, Antimicrobial Drug Development and Resistance, in 04.

DR. ALBRECHT: Renata Albrecht, Director, Division of Special Pathogen and Immunologic Drug Products.

DR. POHLMAN: Janice Pohlman, Medical Office, Division of Anti-Infective Drug Products.

DR. KRAUS: Carl Kraus, Medical Officer, Division of Special Pathogen and Immunologic Drug Products.

DR. RODVOLD: Keith Rodvold, University of Illinois at Chicago.

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DR. FLEMING: Thomas Fleming, University of Washington.

DR. ELASHOFF: Janet Elashoff, Biostatistics, Cedars-Sinai and UCLA.

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

DR. RELLER: Barth Reller, Infectious Diseases, Diagnostic Microbiology, Duke University.

DR. TURNER: Tara Turner, Executive Secretary for the committee.

DR. LEGGETT: Jim Leggett, Infectious Diseases, Portland, Oregon.

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

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

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

DR. PORETZ: Donald Poretz, Infectious Diseases, Fairfax, Virginia.

DR. GWALTNEY: Jack Gwaltney, Infectious Diseases, University of Virginia.

DR. SYDNOR: Austin Sydnor, Retired Otolaryngologist, Charlottesville, Virginia.

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DR. TUNKEL: Allan Tunkel, Infectious Diseases,
Drexel University College of Medicine.

DR. BROWN: Ken Brown, Infectious Diseases,
University of Pennsylvania.

DR. LEGGETT: Welcome, everyone.

Tara, could you please read the Conflict of
Interest.

Conflict of Interest Statement

DR. TURNER: The following announcement addresses
the issue of conflict of interest with respect to this
meeting and is made a part of the record to preclude even
the appearance of such at this meeting.

The Food and Drug Administration has granted
waivers to the following Special Government Employees which
permits them to participate in today's discussions: Drs.
Jan Patterson, Thomas Fleming, and Keith Rodvold.

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

Further, Dr. Jack Gwaltney and Dr. Donald Poretz
reported financial interests in pharmaceutical companies
covered under CFR 2640.202(b) de minimus exemption.

The topics of today's meeting are issues of broad
applicability. Unlike issues before a committee in which a
particular product is discussed, issues of broader

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applicability involve many industrial sponsors and academic institutions.

The committee participants have been screened for their financial interests as they may apply to the general topic at hand. Because general topics impact so many institutions, it is not prudent to recite all potential conflicts of interest as they apply to each participant.

We would also like to note for the record that Dr. Kenneth Brown is participating in this meeting as an acting industry representative, acting on behalf of regulated industry.

FDA acknowledges that there may be potential conflicts of interest, but because of the general nature of the discussion before the committee, these potential conflicts are mitigated.

In the event that the discussions involve any other products or firms not already on the agenda for which FDA participants have a financial interest, the participants' involvement and their exclusion will be noted for the record.

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

Thank you.

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DR. LEGGETT: Thank you.

Dr. Albrecht, could you please give us a general overview.

**General Overview: Antimicrobial Development
for ABS, Regulatory History**

DR. ALBRECHT: Good morning, everyone. I would like to welcome you to the second day of the Anti-Infective Advisory Committee meeting. I would also like to thank the members of the advisory committee, as well as our invited consultants, for being with us today to help us on a number of scientific issues.

This morning you are going to hear a series of presentations on various aspects of clinical trial design in acute bacterial sinusitis, and then we are interested in the committee's and our consultants' advice on several aspects of clinical trial issues in antimicrobial drug development for the indication of acute bacterial sinusitis.

So, to start, I would like to provide a general overview on the antimicrobial development for acute bacterial sinusitis, highlight some regulatory milestones, and talk about the goals for today.

[Slide.]

The first drug that received labeling for the indication specifically of sinusitis was Augmentin, which

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was approved in 1984, and the labeling at the time stated "Sinusitis infections caused by beta-lactamase producing strains of Hemophilus influenzae and Branhamella catarrhalis." That is the former name of Moraxella catarrhalis.

Other drugs that were approved at that time or before that time had more nonspecific wording in the Indication Section, such as for Amoxicillin, "Infections of the ear, nose, and throat," and other products carried a broader sort of indication of upper respiratory tract infections, which may or may not have included infections of the nose or sinusitis, as well.

Approval in those years was based on clinical data and patients on both arms of the study--these were comparative studies--had sinus puncture and aspiration for microbiologic documentation of a bacterial pathogen at entry.

[Slide.]

So, as I mentioned, approval was based on demonstration of efficacy, which included clinical outcome and also microbiological data from baseline pathogens, as well as safety.

The approval took into consideration other relevant data which invariably included in vitro activity on the target pathogens and pharmacokinetic data on the

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product in question, and at least on one occasion, there was also tissue and sinus fluid drug levels available in the application.

Again, the indication was not sought in isolation. It came typically in an NDA where the applicant, the sponsor was looking at multiple indications for approval including a number of respiratory indications, for example, community acquired pneumonia, AECP, acute bacterial otitis media, and non-respiratory indications, such as skin or urinary tract infection.

[Slide.]

As I mentioned, microbiology was a component of the data available on patients and, in fact, baseline pathogens were sought in all patients on both the tests and the control arm.

Now, to document the presence of a bacterial pathogen, a sinus puncture with aspiration was involved, and the agency started hearing fairly early that there was concern about patient acceptance of this procedure. It was invasive, it did involve discomfort, and sometimes, even despite anesthesia, apparently there was some pain.

[Slide.]

So, the FDA, actually in consultation with IDSA in an effort that was going on in the 1992 era, did consider an alternative approach, and this was documented

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in 1992, what is known as the Points to Consider document that was put out at that time by the Division of Anti-Infective Drug Products.

To very briefly summarize, what the 1992 Points to Consider document did is put forth two clinical trial designs that could be used to support this indication. The first has become known as the "Clinical only" trial design. This was a comparative study where rigid criteria clinical and radiographic were used to select a patient population with the expectation that these patients had bacterial sinusitis.

Microbiologic diagnosis was not required and the delta that was used for this comparative study was determined by a step function, which was summarized in the document.

A second study, referred to as a "microbiologic-driven" study, was stated to be open in that document, which was translated to mean non-comparative, and the majority of these studies were not comparative, and patients on the test drug had sinus punctures performed to document the bacterial pathogen at entry.

The purpose of the second study was to try to reduce the number of patients who would need to undergo the invasive procedure, but despite that measure, there was still continued concern about the procedure.

[Slide.]

As a result of that, in 1994, the agency asked the advisory committee to consider whether endoscopic sampling of the sinus to obtain a specimen for culture would be acceptable as an alternative to sinus puncture and aspiration.

During that advisory committee, we heard presentations from FDA consultants, and two of our consultants are actually with us today, Dr. Gwaltney and Dr. Wald, and industry.

After deliberation, the committee actually recommended that sinus puncture should continue to be considered the gold standard, that studies to compare endoscopy to puncture have not really been done. Dr. Talbot did present some preliminary data from his trial at that advisory committee meeting, but other data were not available from the published literature.

Also, the observation was that in 1994, endoscopy was not considered a precise, reproducible and standardized procedure, so the suggestion was that endoscopy continue to be evaluated to see whether it perhaps in the future could have a role in this diagnosis.

[Slide.]

As a result of that, the agency, in putting together the draft guidance documents that we have

available now, in 1998, adopted the trial designs initially put in the 1992 Points to Consider document.

At the present, there are two clinical trials recommended - one, the clinical-only comparative trial where an active control is used as the comparator. In this trial, rigorous case definitions based on signs and symptoms, as well as radiographic findings, should be used to select the patient population.

The recommendation is that patients have more than 7, but less than 28, days of signs and symptoms of an upper respiratory tract infection. The signs and symptoms are listed in your handout and also in the document.

Radiographic evidence of mucosal thickening, air fluid levels, opacification is also requested, and no microbiology is requested in this particular study, and evaluations at baseline, as well as outcome assessments at 1 or 2 weeks post-therapy are based on the clinical criteria.

[Slide.]

The second study, the so-called microbiologically-driven study, is often a non-comparative study, still a clinical trial looking at clinical outcome, as well as microbiological data in each patient.

In this trial, the idea is that again the clinical and radiographic criteria ideally would be similar

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to what was used in the comparative trial, and that the microbiology of the maxillary sinus be obtained through puncture and aspiration at baseline.

That specimen should be examined for the presence of bacteria, as well as WBCs. It should be sent for isolation, culture, and quantification of the pathogen, and although the recommendation of 10^4 colony-forming unit/ml is made for Staph aureus, the thought was to actually try to make it easier to find the common three pathogens. Those, in fact, the agency will consider as pathogens regardless of colony count.

There is a quantitative number of organisms that is being looked for, 25 Strep pneumo, 25 Hemophilus influenzae, 15 Moraxella catarrhalis, and if Staph aureus is being sought, about 10 to 20 isolates should be available.

Again, evaluation is made at baseline and the outcome is assessed at 1 to 2 weeks post-therapy, and the microbiologic outcome or eradication is presumed based on the clinical outcome of the patient.

[Slide.]

So, why are we here today? What is it that we hope to get your advice and guidance on?

We have experience with about 10, perhaps a dozen, NDAs since 1990 where the applicant was looking for

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the indication of acute bacterial sinusitis, and it is time to consider whether the advice in the draft guidance to industry on acute bacterial sinusitis that we have is useful and sound, or is it perhaps time for us to revisit this guidance document.

Specifically, the clinical-only trial, while it is more acceptable to patients, have we actually lost diagnostic specificity by using that approach?

As far as the microbiologically-driven study, are fewer patients really undergoing sinus puncture, which was one of the implied goals in putting forth this study design?

Is the non-comparative data that we are obtaining from this study informative or adequate? Are there other diagnostic procedures that could perhaps be now used in lieu of the gold standard to obtain specimens for microbiology?

As I mentioned, the two trial designs recommended in this guidance, are they yielding reliable data on drug efficacy, or is it time for us to consider other trial designs, as well?

[Slide.]

To address these issues, we have a series of presentations, and we are privileged this morning to have

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Dr. Jack Gwaltney, who will start the presentations with an overview of acute bacterial sinusitis.

Then, Dr. Austin Sydnor will actually show us a video of a sinus puncture procedure, and Dr. Fleming will talk about Statistical Considerations in Clinical Trial Design in Acute Bacterial Sinusitis.

[Slide.]

Then, you will hear a series of presentations by FDA staff. Dr. Kraus will talk about Clinical Evaluation of ABS: Diagnostic Considerations. Dr. Pohlman will review past approvals of drugs for this indication and talk about lessons learned from the clinical trial designs.

Dr. Powers will conclude the presentations with Clinical Trial Design in ABS: Consideration for Future Guidance.

[Slide.]

As you listen to these presentations, keep in mind the questions that we will be asking you to address this afternoon. Dr. Cox will elaborate on these.

Very briefly, the questions will be: How to ensure that patients in clinical trials of acute bacterial sinusitis have bacterial disease, and in that, we will also be asking you to think about how to obtain the microbiological data, whether sinus puncture and endoscopy or other procedures may be useful.

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[Slide.]

The second question will be ask you to discuss the clinical trial design for acute bacterial sinusitis. Some of the areas include strength and limitations of placebo-controlled trials, non-inferiority trials, and also the non-inferiority margin in non-inferiority trials for this indication.

We will also ask about the strengths and limitations of comparative microbiological data.

[Slide.]

The final question that we would like you to keep in mind is to discuss the issue of measuring outcomes in patients in trials of acute bacterial sinusitis. Include in your discussion measuring time-to-resolution of symptoms as an endpoint compared to fixed endpoints.

Now I will turn it back to you, Dr. Leggett.

DR. LEGGETT: Thank you.

Could I have the two other members of the committee please introduce themselves.

DR. CROSS: Alan Cross, University of Maryland.

DR. SUMAYA: Ciro Sumaya, School of Rural Public Health, Texas A&M University.

DR. LEGGETT: Thank you.

I think we will continue and have Dr. Gwaltney present to us an overview of acute bacterial sinusitis. As

we did yesterday, we will have a timer to let the speakers know when it is about time to close up.

Acute Bacterial Sinusitis: Overview

DR. GWALTNEY: Thank you for the invitation to be here today.

Most cases of acute community-acquired sinusitis arise in the setting of a patient that has got either a common cold-like illness or an influenza-like illness.

[Slide.]

When a physician is faced with the management of one of these patients, there are several questions that need to be addressed in order to deal effectively with the problem, and these questions also are relevant to the discussion today because they are important in terms of designing clinical trials of antimicrobial therapy in sinusitis and in selecting a patient population which would be appropriate for use in those clinical trials.

The questions are as you see here. Is disease present in the sinuses? If it is present, is it viral or bacterial? What are the bacteria and the clinician wants to know what antibiotic to select. Here today, the question might be what antibiotic to test and what criteria to use to determine that valid results have been obtained from testing of that antibiotic.

[Slide.]

The first question, is disease present in the sinuses, this question in the past was somewhat difficult to answer because the sinuses are difficult or impossible to examine, they are difficult to sample in a non-invasive way, so the most specific diagnostic test was thought to be some type of imaging procedure.

[Slide.]

This, I think has changed, and it changed because we now know that patients that have common colds and flu-like illnesses also have sinusitis, that this disease is not just a rhinitis, but it is a viral rhinosinusitis.

If patients with early common colds, in this particular study, colds of duration 2 to 4 days, are examined by CT scan of the sinus, these are the kind of findings that you see.

I don't know with the lights, if you can see those CT scans very well, perhaps it is possible to dim the lights up here in the front of the room.

[Slide.]

These are taken from the same patient early in the illness, at approximately 2 weeks later. Some of you may be not be familiar with CT scans. This is a coronal view cut down through the front in this plane. This is a normal examination. The sinus is normally full of air, which is black. Of course, the bone is white.

In this instance where the patient has the acute cold, this gray material in both maxillary sinus cavities and also here in the anterior ethmoids.

I also want to point out these black areas here, and these are air bubbles. This tells you that this is not thickened mucus membrane which you might suspect from looking over there, the way this is distributed around the lumen of the sinus, but that indeed this is some kind of fluid material because of the presence of the air bubbles.

This patient received no antibiotic treatment and, as I said, had recovered from these abnormalities in the sinus in 10 days to 2 weeks.

[Slide.]

Just another example. This patient has disease here in the ethmoids again, a little bit in this maxillary antrum again, clear after the cold is resolved.

[Slide.]

Here is another patient. This slide is in backwards, I am sorry. This sinus has a lot of this material in here. This sinus is completely clear. There is an accessory ostium present in this patient. You can see this material kind of oozing up here as it is transported out of this sinus cavity by the mucociliary transport and again returned to normal. This again is evidence that that is not mucosal thickening.

The distribution of that would also be unusual I think to have so much mucosal thickening here, nothing here, and nothing here. The erratic distribution of these abnormalities was something that was puzzling when they were observed.

[Slide.]

In this study, the summary of the results were that the maxillary infundibulum, the passage that drains the maxillary sinus, was occluded in 77 percent of these patients. The denominator here is 31. There were abnormalities like I showed you in the various sinus cavities - 87 percent maxillary, 65 ethmoid, 32 frontal, and 39 sphenoid.

[Slide.]

So, the answer to the first question is disease present in the sinus really does not require any specific diagnostic test. One can assume that in the patient with an upper respiratory illness like a cold or flu, there is a very good probability that there also is some disease in the sinus cavity. As I said, really, we should look at these diseases as cases of viral rhinosinusitis.

[Slide.]

Now, just a word about what is going on in this process, because when it was seen that the sinuses were

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involved, the question obviously arose what is this abnormality, what does it represent, and how does it occur.

Here is another patient with a common cold and you see the distribution, quite unusual, here in the upper part of this sinus and down here in the bottom here, again, this ethmoid disease.

[Slide.]

Just a kind of graphic representation of what we think this material is. This is material obtained from a patient with an early common cold in which we fished out the mucus, not the thin stuff, but we went and got the good glob of mucus, which I am sure you are all familiar with if you have children or have colds.

We split the specimen and we put it in a syringe, as you see here. Now, the diameter at the end of this syringe is about 3 millimeters. It is about the same diameter as what the infundibulum of the maxillary sinus is. This specimen was left as it was, and in this we put some N-acetylcysteine, a mucolytic, and we left it overnight.

As you can see, with the mucolytic, the material did drain, but when left alone, it was not able to get out of the syringe, and we think this is very similar to what we are seeing happen in the sinus cavity.

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Now, the sinus cavity is lined with goblet cells. There is a very high concentration of goblet cells and not many seromucous glands. The original thought was that maybe by some triggering mechanism, the goblet cells were exocytosing the mucus, but a couple of years ago we saw a patient that had again acute common cold and the sinus was full of this frothy material. You can't see well on the slide, but there are bubbles all the way up through the entire cavity of the sinus.

This is the same patient, a few days later when it is coalesced, you still see there are some bubbles here. This led to the idea that the only thing that made sense was this fluid and the bubbles had gotten into the sinus cavity by being blown down the infundibulum, and that led to the question of what types of actions would lead to the expulsion of material from the nasal passage into the sinus cavity.

We looked at the three most likely types of activities, which were nose blowing, coughing, and sneezing, and working with some engineers who measured intranasal pressure, determined that--and this is intranasal pressure in millimeters of mercury, not water, so this is up in the level of a diastolic blood pressure-- nose blowing does elevate intranasal pressure consistently to these ranges, and the engineers calculated that if the

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middle meatus is loaded with mucus, one nose blow would have the capacity to propel approximately 1 ml of mucus into the maxillary sinus cavity. Coughing and sneezing did not elevate the intranasal pressures much above baseline.

[Slide.]

We pursued this one step further and took more volunteers, put contrast medium in the back of the throat, again had them cough, sneeze, or blow their nose, and every time they blew their nose, we would find the dye here in the anterior ethmoid, here in the infundibulum of that maxillary sinus, here, and here is some in the base of the maxillary sinus with a bubble in the posterior ethmoids and in the sphenoid.

So, it appears that at least one mechanism or maybe the most important mechanism for introducing material into the sinus cavity during these upper respiratory infections is nose blowing.

Of course, nasal fluid during a cold contains not only the virus that caused the cold, it contains inflammatory mediators, and it contains bacteria, and to me, it is really somewhat surprising that the instance of bacterial sinusitis is not higher than it is if the nasal fluid reaches the sinus on such a regular basis.

[Slide.]

Now, the second question is if disease is present in the sinus, is it viral or bacterial. This, of course, is one of the major questions being addressed today is how do you make that determination.

[Slide.]

There are not ideal studies that address this question. The ideal studies would involve sinus puncture of patients with colds at various stages in the illness, and that has never been done.

Probably the two best sets of data that we have, one comes from the Cleveland Family Study, the old study done in the fifties and sixties of some 11,000 patients based on clinical diagnosis. It was thought that 53 or half a percent had developed a secondary bacterial sinusitis.

This is a more recent study by Berg done in ENT patients who were in the clinic, and these patients did have sinus puncture, however, cultures were not done on the material. The diagnosis was based on the observation of the character of the material, and if it looked purulent, then, the diagnosis of bacterial infection was made and 2 of 89 or 2.2 percent of these patients were thought to have bacterial sinusitis.

This I think is probably in the range of what does occur. You have all had colds and you know that

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fortunately, most of the time they don't turn into a bacterial sinus infection, but this also presents a major problem in terms of diagnosis, because with this great disproportion, 98 percent viral, 2 percent bacterial, diagnostic tests have to have high specificity in order to have accurate predictive value.

[Slide.]

Now, the fact that bacterial infection does occur is certainly well established by sinus puncture studies that go back to the late forties and fifties beginning in Scandinavia, and they have been continued in the United States and elsewhere, so there is no question to the fact that it does occur.

[Slide.]

Now, in terms of diagnosis, though, problems remain and when individuals have looked at the sensitivity and specificity of the clinical findings in patients with acute sinusitis--this is a study by Williams and this is a study by Berg--the findings are that these several things that have been considered characteristic of bacterial sinusitis, the individual signs and symptoms, none of them have both high sensitivity and high specificity.

For example, colored nasal discharge where there is quite a bit of sensitivity, the specificity is only 52 percent.

Maxillary toothache, which occurs in the patients in which the pathogenesis of sinusitis begins with the infection of the tooth root, not a cold or flu-like illness, this has quite high specificity, but only a very low sensitivity because most patients develop the sinusitis from the cold and flu, and not from the dental infection.

The same thing was seen by Berg, who again was using sinus aspirate and looking at the purulent character of the material.

[Slide.]

Another diagnostic approach has been the use of x-ray. That slide apparently didn't fall the way, but this is from a study, that was the first study that was done by the Charlottesville group in 1975, in which punctures were done and x-rays, not CT scans, were compared.

This led to the findings which were described earlier, that the air fluid level, the thickening of the mucous membrane, quotes thickening of 3 ml or more, I think that is all right, or a complete opacity.

As you can see, the number with positive culture here with the air fluid level was relatively high, and I want to talk about that in just a second.

The number with positive culture, here is the denominator and the numerator. It was not as good with quotes mucosal thickening or complete opacity. I also want

to point out that these patients had been through a filter. They were in the ENT clinic, so they had been ill probably for a week or longer in most cases. This would not be what you would find if you did this study in patients that were early in a cold-like illness.

[Slide.]

This is just an x-ray from back at that time, and here is an air fluid level right here, and this is what we are talking about. This is a very flat meniscus, and this is characteristic of patients that have thin fluid in the sinus cavity. If you put this patient in a different position, that fluid would move, unlike the material I showed you with the viral rhinosinusitis.

What may happen in these patients is that the thicker material with the viral infection is degraded by bacterial enzymes--this is just a speculation--and you get this thin material, and that is why that is more specific for the bacterial infection.

[Slide.]

Another approach that has been looked at more recently is to do endoscopic sampling of the nose, and I want to emphasize that this is the nose, not the sinus cavity. It is not possible to insert an endoscope into the sinus cavity because of the protected nature of the infundibulum and the acute angle that occurs.

So, the best that can be done is to put the endoscope into the area where the sinus cavities drain. In this comparative study, which was mentioned earlier, if all cases were looked at--the new technology is overriding my old horse and buggy slides, I am sorry, but if it doesn't work, I can show you the slides and you can pass them around.

These are just the data I talked about earlier.

[Slide.]

This is the Talbot study. This was a head-to-head comparison, the same patients that had both endoscopic sampling and sinus aspiration, sensitivity 65 percent, specificity 40 percent, positive predictive value 38, negative 67, accuracy 49, which is obviously not very good.

If only the three organisms were examined, then, the accuracy was 85 percent. By doing this, one leaves out other important pathogens, such as the anaerobes, the alpha-hemolytic Strep like Strep milleri, Strep intermedius, or pus-producing alpha-Strep, beta-Strep, and Staph aureus.

[Slide.]

So, there are problems in establishing a diagnosis of acute bacterial sinusitis, and these are that the signs and symptoms do not have a desirable degree of specificity for making the diagnosis, and the standard that

has been used in those studies, or in Williams' study, was imaging. This is a very important point - the correlation was not made with sinus puncture, and as I have said, neither has imaging been correlated with the results of sinus aspirate culture.

So, there are two problems with trying to understand the results of that study, and it was certainly a well done study in the sense of what it was possible to do under the conditions of the study, but there are problems because of the lack of what would be an acceptable diagnostic standard for bacterial sinusitis, which is a positive sinus aspirate culture. That is the way we diagnose infectious diseases, and it is for other types of infections, and the same should be true for sinus infection.

The signs and symptoms have not been correlated. This study has never been done with pretreatment of bacterial sinus aspirate culture. Signs have not been correlated with post-treatment bacterial sinus aspirate culture.

We don't know whether this assumed bacteriologic cure based on the clinical course really has any validity, because there are no data to show that such a correlation exists. Neither has imaging been correlated with pre- and post-treatment sinus aspirate culture, and diagnosis of

bacterial sinusitis in clinical trials have been based on these signs and symptoms of imaging.

Now, I might also say that in terms of the endoscopic sampling, as far as I know, there are no data on whether that correlates with the result of bacteriologic cure after treatment. So, that also is a problem.

[Slide.]

Well, now, in order to help the clinician to make a diagnosis, these three categories have been proposed of patients presenting who may have acute bacterial sinusitis.

One is an emergent category, which fortunately is quite rare, which is sinusitis that has become complicated by bacterial meningitis or brain abscess. These patients present with either orbital or periorbital infection. The attention of the more serious illness usually is what brings these patients in.

There is a second category here termed "urgent." Patients that have what has been the classical description of acute bacterial sinusitis, fever, erythema over the cheek, true pain, real tenderness, and maxillary toothache in those patients that have dental infection that is the initiating factor.

These patients, if presenting this way, should be diagnosed as having a bacterial infection of the sinus cavity, in most cases, don't have this, and therefore, they

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are in what would be called an elective category here, and these are patients that have a cold or flu-like illness which is no better or worse after 7 to 10 days.

This is currently pretty much the standard that has been proposed by a number of expert groups to be used by clinicians in the diagnosis of bacterial sinusitis. What is this based on? It is based on indirect evidence.

I guess the best evidence is that in studies which we did in Charlottesville, in patients that were in this stage of the illness, about 60 percent of them would have a positive aspirate culture. They would have bacteria growing in the aspirate culture and frequently in titers of 10^5 , 10^6 , or 10^7 .

[Slide.]

The other piece of information or the other inference that could be made is that if you look at the duration of patients with known viral colds, and this bar graph is from patients in an insurance company, 139 patients who had proven rhinovirus colds by viral culture, and this is the duration of illness, you see that the majority of these patients have gotten over the illness, they are completely well by, say, 8 to 12 days, so the great bulk of patients with an uncomplicated cold will be well and certainly an even higher percentage will be better at the end of the 7 to 10-day period.

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The other reason to believe this is Dr. Ellen Wald thinks it is true, and I give her great credit for being an authority in this disease, as well. I kind of came up with the same belief.

[Slide.]

The third question, what are the bacteria, and this is a question that is easy to answer, based on the sinus puncture studies that have been done over the last 50 years, the etiology is as shown here, it hasn't changed, pneumococcus, Hemophilus influenzae, and about 50 to 60 percent, sometimes more than one pathogen is recovered in the aspirate culture.

The anaerobic bacteria in the patients that have dental disease, and then Moraxella, and I am sure this percentage is too low, because in more recent studies when Moraxella was recognized as a pathogen, usually, these were discarded and called Neisseria as you heard Dr. Albrecht say, and then Group A Strep, and then other Strep species that I mentioned, and again I think this is an underestimate, these are an important cause also.

Staph aureus does cause acute community-acquired bacterial sinusitis, but a relatively small percentage, absolutely a small percentage.

Finally, what antibiotics to select.

[Slide.]

Well, the question that I think should be addressed before that question, and really I won't get into that today because that is not appropriate for this group, is this question here. Should cases of acute community-acquired bacterial sinusitis be treated with antibiotics?

If the answer to that is no, then, really, there is no reason for us to be here today, and there are people around the world who would substantiate that, who would support this proposition.

That has fairly recently been raised. I have to say that I wonder why sometimes these kind of ideas are proposed, but I think you cannot argue with the fact that without there ever having been a placebo-controlled clinical trial with pre- and post-treatment of sinus aspirate cultures, you really can't criticize somebody who would raise that question.

[Slide.]

Well, to answer that question, one has to answer two other questions: Is acute community-acquired bacterial sinusitis a disease? If it's not a disease, then, obviously, you don't need to treat it, and if it is a disease, is antimicrobial treatment effective?

[Slide.]

Well, the question of is it a disease, there were a number of studies done in rabbits in which the sinus

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cavities were artificially infected and then histopathologic studies done, and they showed damage to the sinus cavity, particularly to the epithelium.

More recently, as far as I know, really, one of the first or maybe the first study that was done in humans was published in 2000, and in this study, the epithelium was intact in most sections, but pathologic changes were found in the lamina propria, and these include edema, massive infiltration of neutrophils, increased lymphocytes and plasma cells, microabscesses, thrombosed blood vessels, and necrotic foci.

So, I think this is pretty sound evidence that this process is a disease, these are not normal histologic findings.

[Slide.]

In summary, one could say that there are several things that support the idea it's a disease. Number one, the sinus is normally sterile and during this condition, there is loss of sterility and bacteria are present in high quantities in association with evidence of inflammation in the form of white blood cells.

Pathologically, there is destruction in the lamina propria, not the epithelium. This is in the rabbits. Physiologically, there is impairment of sinus clearance, so the sinus is not doing what it is supposed to

do, whatever that is, and then the risk status--and this is never discussed by people who talk about not treating patients--but there is an increased risk of susceptibility to the central nervous system and orbital infections, as I mentioned, and although it is small, when it does occur, this is a serious and sometimes catastrophic illness.

[Slide.]

So, if one assumes that it is a disease, and the theoretical reasons to treatment patients with antibiotics would be to restore sterility to the sinus cavity, reduce duration of illness, prevent the complication, and prevent progression to chronic sinus disease.

I have to say that I don't think there is good evidence to expect that this might occur because the pathogenesis of chronic sinus disease is certainly not understood, and I think some people think that maybe it is an entirely different process and that acute sinus infection may not be a risk factor.

On the other hand, we don't know that it is not a risk factor and so I certainly think it needs to be considered in the deliberations.

[Slide.]

Well, now, what would be the features of a clinical trial that would be desirable? This is my attempt to list what I think would be important.

Content validity. Ideally, a positive pre-treatment of sinus aspirate culture and a quantitative culture would be preferred because there are some bacteria where there might be some question about whether they were actually pathogens or not, although with the Big 3 mentioned, if you grow them at all, then, I think it is reasonable to accept them as being pathogens. It would be nice to have simultaneous Gram stains.

In the absence of this, probably the next best thing that could be obtained would be a positive history of a common cold or influenza-like illness that is no better or worse after 7 or 10 days, the clinical criterion, not the gold standard, but at least something that seems to have some validity.

The other things are pretty standard. You would like the sample size calculations to be done and reported, and be adequate for the effect size as specified, randomization of the patients, blinding, patients and investigators, look at the completion rates, look at compliance.

[Slide.]

And then the endpoints. Bacterial eradication, and ideally, this would be based on post-treatment sinus aspirate culture again with quantitative culture because some patients, their culture may not be entirely sterile,

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but if the titer is dropped a number of logs, one could assume that the patient is going to undergo a cure.

Clinical response based on pre- and post-treatment standardized measurements, and this has been done in a number of trials. It would be nice to have imaging evaluations, as well, and then nowadays it is always important to put on the functional status of work, daily activities, things like this, and, of course, proper analysis of the data.

[Slide.]

This is a review of nine studies that were done and are in a paper which I think is material you have received and will be published in the journal Clinical Infectious Diseases in January.

You see the studies listed here. They were evaluated for content validity, sample size, calculations, randomization, double blinding, standardized measurements pre- and post-imaging evaluations.

As you can see, five of the studies did have imaging as part of the experimental design. All were randomized, all except one had double blinding. All except one had randomization. So, in terms of the quality of the experimental design, you would I think say that this part was handled very well.

[Slide.]

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Again, the same, going backwards now. Sample size calculations were done in only 3 of these 9 studies, but, of course, if you have a positive finding, then, that would be less of a problem. But when you get to the first of these criteria, the content validity, then, the studies fall down badly.

Looking at the clinical standard of duration of illness, the only study that probably meets that is Lindbaek study, and although that is not in the paper, in discussions with him, he did say most of his patients had been sick for a week or longer.

In this study, the patients had had symptoms for five days. None of the studies had sinus aspirate cultures although the old study by Rantanen did take sinus aspirates, but there were no post-treatment culture results reported in that particular study.

So, this obviously is an important point now that we know of the existence of viral rhinosinusitis because if you are not really studying what you think you are studying, then, obviously, you can't hope to get valid results from your investigation.

[Slide.]

Well, what information is available from non-controlled studies?

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First on the question, does antimicrobial treatment eliminate infection, a number of pre- and post-sinus aspirate culture uncontrolled studies have been done. We did a number of these, here through '75, and that should be 1997, not 77, number of antibiotics.

When these studies were done, resistance had not developed in Hemophilus and Moraxella, so these were appropriate antibiotics. They were given for a 10-day course, and if you look down the list, you see that the resolution rate was in the range of 90-95 percent.

I want to point out that is the wrong word up here. I made the slide, but it really should not be cure, we can't claim that these were cures because we had no control group to make any comparison to, and all we can say is a resolution rate. But I think you can say that if patients with this disease, which is proven by bacterial culture from the sinus, are given antibiotics, that approximately 90 to 95 percent will no longer be infected after 10 days of treatment.

[Slide.]

Now, is there any control information on this? There is an old study by Carenfelt done in 1975, in which patients were evaluated based on whether the antibody concentration in the sinus aspirate was greater than that of the causative bacteria, and if that were so, the

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eradication rate was 90 percent compared to those in which the concentration of the sinus aspirate was less than that of the MIC of the causative bacteria and a cure rate of 45 percent. This is a significant difference.

We did a study a number of years ago in which we were looking at clindamycin, which is not effective for *Hemophilus influenzae*, and we stopped the study because that was obviously not a good idea, but we had zero of 6 cures in patients receiving clindamycin who had *Hemophilus influenzae*. You compare that to the rate that I showed you earlier. This is a significant difference.

[Slide.]

Two other studies that are published that I know of, again, a study from Scandinavia, an appropriate antimicrobial and dose, and a suboptimal dose, and in all three studies--this was cefaclor at a dose of 500 milligrams either b.i.d. or t.i.d.--and a cure rate 91 percent versus 74, and 90 percent versus 20, and 71 percent.

So, there is limited data on bacteriologic eradication based on pre- and post-sinus aspirate cultures.

[Slide.]

This is just a Gram stain from one of the patients that had *H. flu* and got clindamycin, and after 7

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days, you can see this is still a very diseased sinus with all the Hemophilus influenzae and the pus in the sinus.

[Slide.]

Does antimicrobial treatment reduce disease?

Looking at the papers that I showed earlier, and there are only eight here because in one of them, it was difficult to extract the clinical information, this is the improvement of illness, and this is not necessarily resolution, but improvement in patients on placebo.

We have no studies of the natural history of this disease in untreated patients with acute community-acquired bacterial sinusitis the day of evaluation from one to two weeks, and this is the number improved over the number observed. As you can see, the range was from 37 percent to 79 percent, and this had a mean improvement rate of about 60 percent.

[Slide.]

I think the best study or at least the only study that did try to use a criteria of duration of illness was the one by Lindbaek, which is published in the British Medical Journal. This was a double-blind, controlled trial. This looks at the proportion of sick patients, and this is days. This is a placebo group, and this is the two groups treated with antibiotics.

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This was with high-dose penicillin and with amoxicillin, and here, at about two weeks time, the improvement or actually the resolution rate is in the range of about 50 percent, similar to what was seen in the studies I just showed you.

[Slide.]

So, in summary, in my opinion, the current status of testing the effectiveness of antimicrobial treatment for bacterial sinusitis is not satisfactory, and it is due to the problems in making a bacteriologic diagnosis and determining bacteriologic cure.

I don't think this is surprising, it is certainly understandable. The use of sinus puncture has been considered invasive and has, in many people's minds, been considered not an appropriate thing to do even in the investigative setting.

Also, information on clinical response in relation to bacteriologic response is lacking.

Thank you.

DR. LEGGETT: Thank you, Dr. Gwaltney.

Does any of the panel have any questions regarding his talk? Yes, Ken.

DR. BROWN: Dr. Gwaltney, I think this is a fantastic presentation.

Is there good evidence that treatment with antibiotics, whether approved or not, is better than a sinus puncture for relief?

DR. GWALTNEY: You are saying is the old treatment of sinus puncture and washing, which was done for centuries, is that better than antimicrobial treatment?

DR. BROWN: No, I am saying is antimicrobial treatment better than that?

DR. GWALTNEY: Either way. I don't know.

DR. BROWN: I know, as a person who has had a puncture repeatedly, I will take the puncture any day for relief.

DR. GWALTNEY: Well, Dr. Sydnor is sitting next to you, and you can certainly call him if you need him. That is certainly a very good question, and it has never been investigated, so we don't know the answer.

I personally believe that washing is very effective, and in patients who fail a course or two of antimicrobial treatment, I would send them for that immediately because if it is a risk factor for chronic sinus disease, I would like to eliminate that because that can be a very bad and life-long condition.

So, a good question. We don't have the answer.

DR. LEGGETT: Dr. Gwaltney, looking at different lengths of therapy, recently, there have been antibiotic

trials in community-acquired pneumonia giving five days of therapy. There have been approvals with one dose of a drug or three days of a drug versus what we have always used as sort of the 7 to 10-day course.

Do you know of any data about different lengths?

DR. GWALTNEY: All the data I showed you are based on 7 to 10 days. That is what we have the information on. It wasn't too long ago that people were saying you ought to treat for 21 days, and that was based on the fact they said, well, you washed the sinuses when you took the specimens out, and you were giving the added therapeutic benefit of the sinus wash, so you probably should treat longer because all the patients had not had complete resolution of infection. Sometimes we would still find some bacteria there.

Things suddenly changed. It is a lot cheaper to give 3 days than 21 days, so now, driven by these economic concerns, people are talking about short-course therapy. As far as I know, there are no data based on double tap studies to support that.

In some of the studies that have been published, there was one in JAMA a few years ago, trimethoprim sulfa. I have a strong suspicion that that patient population was contaminated with cases of viral rhinosinusitis, so I don't think it would be proper to change what is an established

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state of the art in terms of duration of therapy without scientific evidence or research studies to support the fact that the short course of therapy may be better--I mean may be sufficient, and it may be.

I think we are going to hear something about that later in the afternoon, which is interesting in that regard.

DR. LEGGETT: Dr. Cross.

DR. CROSS: We know that in cases of pneumonia, resolution of the chest x-ray often lags behind the cure of the disease. What do we know about the case of "adequate" therapy of sinusitis?

DR. GWALTNEY: There is one study, I didn't put it in today, but I think it's a pretty good study in which patients with what seemed to be bacterial sinusitis, although it wasn't a puncture study, were followed by serial MRI.

What was seen was that the changes that are there resolved fairly rapidly or started to resolve over about 10 days, but they didn't clear for up to a month.

So, it looks like that the duration of illness in bacterial sinusitis, in terms of the sinus returning completely to normal status, may be quite prolonged, as long as one month, and that is one of the reasons that some of these studies that I have reviewed, some of them had

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findings of patients that a large proportion had cleared within, say, 10 days, and that tells you that wasn't bacterial sinusitis, that was viral rhinosinusitis.

DR. LEGGETT: Dr. Reller.

DR. RELLER: Dr. Gwaltney, in your design of clinical trials, you had two options of microbiological criterion or 7 to 10 days of symptoms.

Would there be utility of combining those to increase the likelihood of having a positive culture, or alternatively, could you sample too early in the process and before the bacterial infection had been fully established on top of a viral rhinosinusitis?

DR. GWALTNEY: I think in a study in which sinus aspirate culture was part of the design, it would be desirable to have, as an entry criterion, that the illness had been present for at least 7 to 10 days, something in that range.

I feel pretty confident it would increase the yield of patients that were positive for bacteria, but we would also learn something about the validity of this clinical criterion which we are currently using today, bacterial sinusitis. I think we have to start saying bacterial and viral.

DR. RELLER: The second question is rendering an expert opinion. Many people use the change in color,

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persistence and changes colors to say, oh, that is where the transition has gone to bacterial infection and what triggers antibiotic therapy.

Is that of any utility or is it worthless, and that is just the natural history of resolution of the disease when one blows this stuff out?

DR. GWALTNEY: I think the general opinion is that it is not a useful criterion because we say, well, colds can give you colored nasal discharge, but to be perfectly honest, until the study is done where that is correlated with the results of sinus aspirate culture, we really don't know.

When that criterion is correlated with radiographic positivity as a standard, it has poor specificity, so it probably is not very specific, but the real answer has never been determined.

DR. LEGGETT: Don.

DR. PORETZ: For the purpose of designing future studies, should the sinusitis or acute maxillary sinusitis associated with viral respiratory infections be separate and distinct from those of dental origin when you are planning studies? Are they different diseases?

DR. GWALTNEY: I think, well, I think it might be very useful to analyze the results of a study. I am not

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sure I would exclude those patients because I think it would be worthwhile to know what they look like.

They have, as you know, very complicated mixtures of anaerobic bacteria. We have had cases that had four different species of anaerobes and four of microaerophilic species, and that really in many ways is a different kind of infection, and they really respond pretty well to antibiotic treatment and also making sure that the dental disease is corrected with a root canal or something like that.

So, I think that would be a good thing to do. It is a question of getting enough numbers of those kind of cases to have meaningful results.

DR. LEGGETT: Ciro.

DR. SUMAYA: In the information you presented on I believe it was the CT scans of the viral or rhinosinusitis, and you showed a number of changes early in that diagnosis.

Do you have a sense of the frequency of those same CT type scans at 7 to 10 days?

DR. GWALTNEY: Well, in the patients with the common colds, at 7 to 10 days, most of the time those findings had improved or resolved.

DR. LEGGETT: John.

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DR. BRADLEY: If there were an easy procedure to actually tap the sinus to give you the bacteriology that you are asking for, and you had the ability to do these follow-up taps, do you think that the best time to do a follow-up tape in a study for purposes of documenting microbiologic evaluation of eradication would be at 3 to 5 days after therapy, 5 to 7, or 7 to 10?

DR. GWALTNEY: Dr. Jack Anon is here in the audience and is going to talk about what I think is a pretty ingenious approach to this problem after lunch, and I don't want to steal his thunder, but maybe--Jack, should I go on and say what you are going to talk about? I am not going to go into details, or shall we just wait? Save it, he wants to surprise you. He wants you to come back.

DR. BRADLEY: The question is the timing.

DR. GWALTNEY: Well, he is going to address that, and that is a very good question, and they have come up with I think kind of an ingenious way to address that problem.

DR. LEGGETT: Ellen.

DR. WALD: Just a comment in response to Barth's question about the timing of the sinus aspirate and maybe in part to John's comment.

I think for patients who represent the majority of patients, those who present with protracted respiratory

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symptoms as a signal that they have bacterial infection of the sinuses, then, I think you want to do that tap not ever before 7 and maybe as close to 10 as possible.

For patients who present with a more urgent, even though they are not emergent, then, I think you need to do the tap earlier because you need to treat earlier. One question would be whether you want to include both of those patients simultaneously in clinical trials, because they do represent somewhat different populations although I think the bacteriology is the same and their response to antibiotic would be the same.

Just one comment on the color. I mean my supposition is that probably many viral upper respiratory infections go through a phase of transient bacterial infection, but it is transient and we don't need to know about them.

Maybe that is what correlates with the color change, but they go from clear nasal discharge to colored nasal discharge to clear again in the course of a viral URI and maybe what that represents is this transient period of some partial obstruction of the sinus ostia, so there is a replication of organisms to an important height, but then the inflammatory response in the mucosa begins to resolve, the sinus opens again, and drainage is facilitated.

DR. LEGGETT: John.

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DR. POWERS: I certainly want to make a comment relative to what Dr. Wald just said. As Dr. Gwaltney said, there is no data on correlating what color actually means in this disease, the color of the discharge.

If you look at other diseases, there are some natural history studies on acute bronchitis and what this actually means, and if you look at people that have a viral acute bronchitis, they do exactly as Dr. Wald said.

They go through this, the first two days they have no sputum at all, and then it becomes clear, and then it becomes green, and if you eat a purple popsicle, it turns purple, so correlating the color with what is actually going on is very problematic without the bacteriologic diagnosis to go along with it.

DR. LEGGETT: For what it is worth, a lot of the cells in AECB turn out to be eosinophils when the color changes.

DR. ANON: Jack Anon, Clinical Professor, University of Pittsburgh School of Medicine. Jack, as always, you raise questions and bring things to our attention that are key in our understanding of the disease.

There are a couple of things, one of which is your slide, in the beginning, which had your emergent, urgent, and then your third category of sinusitis, I think that for the committee, that may be very important because

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as we did in our sinus guidelines that you were involved with, Ellen Wald was involved with in some early work, what we believe is that there are those patients--the emergent disease, I don't think we need to talk about--but those patients with the group of symptoms in your urgent category, the ones that are ill, the ones that will undergo a sinus tap for relief, those of us who have family members or ourselves who have had this problem, those are the patients where we really ought to be looking at directing antibiotic therapy aggressively.

I think most of us would have no reservations about treating those patients, and it is the third patient, that mild group, that viral in between, gee, is it viral or bacterial, where a lot of the issues are clouded because we can't differentiate at times readily those patients.

So, those are I think important categories that you went over quickly, but may be more important here.

The second thing is with regards to color, we actually have developed a color slide kit similar to what was done in the acute bronchitis study that Dr. Powers was mentioning, and actually I think that it is probably odor that may be a key here.

We actually did a study where we did gas chromatograph studies of Strep pneumo, H. Flu, M. cat, and

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we have plots showing that they have their individual odor characteristics on chromatography.

So, when the patients say, gee, it is starting to really smell, my breath stinks, we actually proposed to this company that we could develop a small mask. They could actually a portable gas chromatograph unit that would fit in an office. You can actually breathe through it and it would give you peaks showing whether or not the bacteria they are producing, their characteristic signatures.

DR. LEGGETT: Dr. Anon, could I please ask you to reveal any potential conflicts of interest as part of speaking here at the meeting?

DR. ANON: Oh, yes, sir. I do consulting work and we are involved with drug companies, such as GlaxoSmithKline, Ortho McNeil, Bayer, Aventis. These are groups that, as an otolaryngologist, we are frequently asked to do consulting work like this with them.

DR. LEGGETT: Thank you.

The next speaker and presenter is going to be Dr. Sydnor, who is going to describe a sinus puncture to us.

Description of Sinus Puncture

DR. SYDNOR: Thank you for asking me to make this presentation. It will date my age and training, but I was trained in the era in which sinus puncture and lavage was really the standard therapy for acute maxillary sinusitis.

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The amoxicillin and ampicillin had not been marketed by the time I was in my training to give you an idea of how far back that goes.

Therefore, to wash a sinus or to aspirate it was a relatively simple procedure that was done by almost all otolaryngologists in private practice back until the advent of endoscopic sinus surgery and the insurance reimbursement thereof.

What we used to do, and still do, and I did a lot of the sinus punctures in Jack Gwaltney's study, would be, the mechanics of it, simply spray the nose with ponocaine [ph] and a decongestant, Afrin or neosynephrine, and then put a topical anesthetic into the inferior meatus of the side of the nose you are going to wash, and we used to use 10 percent cocaine. That has fallen out of favor and now is a combination of lidocaine and phenylephrine, which really I think is a good anesthetic.

We do not inject the mucosa directly with the needle, but then put a needle through the inferior meatus of the nose, directing it posteriorly and superiorly until you feel it go through the bone, and generally up high in the antral sinus, the superior medial wall of the antrum is very thin and you generally can go through without any great deal of difficulty and without pain.

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I have had my sinuses washed several times, I have done my own family, and it can be done without any significant discomfort to the patient, certainly no worse than having a dental filling done even under local anesthesia.

The complication rate is negligible. You probably with forceful--not probably, I know I have done it, anybody who has washed enough sinuses is bound to have some complications. You can go through into the orbit, can come out in the cheek, but that instance is extremely low and in all of our studies, we have had none of this happen.

In the studies that we have done with Dr. Gwaltney, when you put the needle in, we would aspirate it, and if you get pus back, don't wash the sinus because we are trying to test the efficacy of antibiotics, and not the lavage itself, and then get the cultures and the Gram stains, that sort of thing.

If you can't get anything back, then instill about a cc or 2 of normal saline in, kind of stir up the sinus, and aspirate that back.

We have got a video now done from Sweden, an instrument called a SinoJect, that Dr. Anon will talk about later, and that shows basically how the sinus puncture and aspirate is done.

We can go on with that now.

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[Video.]

DR, SYDNOR: That is through now. That is basically how previous studies have been done without the SinoJect, but the principle is absolutely the same without using the forceful instrument itself.

Thank you.

DR. LEGGETT: Dr. Sydnor, what is the variability in the size or the shape of the maxillary sinuses, and is this procedure usually done without any radiographic technique before doing it?

DR. SYDNOR: I think the capacity of the maxillary sinus is about 30 cc, I may be wrong there, but you can use it with or without radiographic evidence if you are treating someone clinically. If you are in a study, it depends on what the protocol calls for.

DR. LEGGETT: Jan.

DR. PATTERSON: Is the puncture enough in some cases to treat the patient, or do you have to do irrigation, as well, if you are going to use that as therapy?

DR. SYDNOR: That depends clinically again if you are treating the person, and also again if you are in a study, what does the protocol call for, repeat aspirate or not, post-therapy aspirate. But prior to any study being

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done, you could use your clinical judgment as to whether it needs to be repeat aspirate or not.

DR. LEGGETT: Dr. Gwaltney.

DR. GWALTNEY: I think the question is in order to get therapeutic benefit, do you need to wash in addition to just do the puncture.

DR. SYDNOR: No, no, I don't think so.

DR. GWALTNEY: The old therapeutic procedure was once you got the thing in there, then, you washed it out.

DR. SYDNOR: Yes, I think clinically, that improves the resolution of the disease certainly from the patient's standpoint. Any of you who have had sinuses washed, know it actually feels good when you leave. I don't mean to compare it to a thrombosed hemorrhoid, but it is not unlike that.

DR. LEGGETT: Thank you, Dr. Sydnor.

Our next presentation will be by Dr. Thomas Fleming, who will discuss Statistical Considerations in Clinical Trial Design in Acute Bacterial Sinusitis.

**Statistical Considerations in Clinical
Trial Design in ABS**

DR. FLEMING: Good morning. I would like to discuss some design issues in acute bacterial sinusitis trials and my statistical colleagues on the committee were

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criticizing me for not preparing a video for the statistical issues, but I will do the best I can here.

[Slide.]

What I will do here is actually just begin with a very brief review of some issues that we discussed yesterday given that we have a number of people here today that weren't here yesterday, talking about issues surrounding criteria of endpoints and surrogates, and then focus more on discussion of non-inferiority issues and time to event analyses for resolution of symptoms to lay some background for some of the issues that we will be discussing in the questions later on today.

[Slide.]

So, very quickly, criteria for study endpoints. Indeed, whereas endpoints should be measurable and interpretable and certainly sensitive, one of the critical criteria here is they should be clinically relevant and clinical efficacy endpoints, endpoints that unequivocally reflect tangible benefit to the patient would be very important measures to have in pivotal studies.

In acute bacterial sinusitis, resolution or improvement of ABS symptoms or reducing time to resolution would be examples of clinical efficacy endpoints.

[Slide.]

Frequently in trials, replacement endpoints are considered surrogate endpoints, and often the approach is to look biological markers that are correlated with clinical efficacy endpoints and then establish effect on those markers.

[Slide.]

However, if we establish treatment effects on markers, such as microbiological and radiological outcomes, whereas those provide very important insights about the biologic activity at intervention, it may not follow that the clinical efficacy measures have also been impacted.

[Slide.]

We discussed this paradox yesterday at some length and let me just briefly review one of the slide to give some insight into this paradox as to why it may be that effects on a marker may not reliably predict the effects on a true clinical endpoint.

[Slide.]

We noted, first of all, that a disease process could have several pathways through which it actually influences the clinical endpoint, and the surrogate may only be in one of these pathways.

For example, if the intervention affects a different pathway, we could miss the effect of the intervention. We talked about chronic granulomatous

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disease yesterday with gamma interferon, which did, in fact, have a positive effect on preventing infections, reducing the rate of infections, and yet didn't have an effect on the expected marker, which was bacterial killing and superoxide reduction, which was a case of a false negative conclusion by reliance on a surrogate.

If the intervention has an effect on the pathway through which the surrogate is capturing effect, we still could get false positive conclusions. We may have decolonization through that pathway, but not other pathways, and so the endpoint may, in fact, not be affected, the infection endpoint may not be affected.

Also, the intervention may have unintended pathway or effects directly on the clinical endpoint, and by being unintended, often would be undetected unless one actually establishes directly the effect on the clinical outcome/

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As one example, we were looking at the example of AIDS patients with MAI bacteremia. A study in 1994 showed that clarithromycin at higher doses had a very clear effect on bacterial loads, substantially lower bacterial loads at higher doses, and yet, the mortality rates were much higher at those higher doses.

So, clarithromycin, in fact, did have a beneficial effect or had a positive effect on bacterial load, but the ultimate effect on mortality was adverse, presumably through unintended mechanisms, that were also existing.

[Slide.]

So, how does one validate a surrogate?

[Slide.]

In essence, just to remember the key for a valid surrogate is we would want the effect of the intervention, of the antimicrobial intervention on the true clinical endpoint to be reliably predicted by the effect of the intervention on a microbiological or surrogate endpoint.

[Slide.]

We had noted that there were two sets of criteria. One of the criteria, both of which must exist, is that the surrogate is correlated with the clinical outcome, but that it, in itself, while it is the necessary condition, it is not sufficient in its own right. One must also show that the surrogate endpoint fully captures the net effect of the treatment on the clinical outcome.

In fact, this is must more often a much more difficult condition to show and, in essence, what we have noted is that a trial of sufficient size to directly show

the effect of the treatment on the clinical outcome is, itself, not sufficient information.

[Slide.]

One, in essence, needs a meta-analysis of multiple trials typically to have the information required to be able to show that the surrogate is fully capturing the effect of the intervention on the outcome.

Clinical insights are also critical. It is important to have a comprehensive understanding of the causal pathways of the disease process and of not only the intended, but what is the likelihood of unintended mechanisms that could also directly influence the outcome.

[Slide.]

So, an acute bacterial sinusitis, one example of a clinical endpoint would be from a patient's perspective, to have timely resolution or improvement of symptoms. Potential markers or surrogates would be radiological and microbiological outcomes, and these certainly provide very important evidence of biologic activity.

We saw in Dr. Gwaltney's presentation that the symptoms themselves are not correlated with pre-treatment or post-treatment bacterial sinus aspirate cultures. A separate question is whether or not the bacterial eradication is, in fact, correlated with resolution of symptoms.

I understand from his presentation and other data that there is rather limited data on that. Even if, however, we had conclusive data showing that if we had bacterial eradication, we have correlation with resolution of symptoms, that itself still is not adequate information to justify or validate the correlate.

We would have to know that the antimicrobial intervention effects on resolution of symptoms are fully mediated through that bacterial eradication, and that is much more challenging conclusion to be able to reach.

Well, let's suppose that we are proceeding then with endpoints of resolution of symptoms.

[Slide.]

What I would like to do now is turn to the issue of how do we assess efficacy in a non-inferiority trial. Essentially, if we are looking at a new antimicrobial against a standard antimicrobial, I think we are all fairly clear how we would show superiority.

We would want to see a higher rate of success on this new antimicrobial. A non-inferiority trials says, well, it is adequate to be the same or better. We just want to rule out that we are meaningfully worse.

So, if we have known rates of success on our standard antimicrobial, let's say 80 percent success of resolution of symptoms at 7 days, we want to be able to

rule out that the experimental antimicrobial has a meaningfully worse rate.

Now, of course, what is meaningfully less? Five percent less, 10, 20? That is the essence of the margin. How do we determine the margin, which is critical if we are going to do a non-inferiority assessment?

[Slide.]

Well, let me begin before getting to the specific issue of the determination of the margin, just to step back and say there really are dual goals that exist if you do a non-inferiority trial.

The first goal is to be able to obtain a direct evaluation of the relative efficacy of the experimental antimicrobial against the active control. So, if we have a standard antimicrobial, we surely would like to know just from the perspective of which of these should I use, what is the relative efficacy of these two.

A non-inferiority trial is excellent in giving us a direct insight into that relationship. But the non-inferiority trial also, from a regulatory perspective, provides other key insights and it contributes to the evidence of the efficacy of this experimental antimicrobial against a placebo.

But in a non-inferiority trial, that placebo doesn't exist, so we have, in essence, what is called an

imputed placebo. What we get from the non-inferiority trial is direct evidence of the experimental antimicrobial's efficacy against the active control, so we need to know something about how the active control would compare to a placebo to ultimately understand how the experimental would compare to a placebo.

So, that means there are certain important conditions that must be satisfied by the active control to be able to do a non-inferiority assessment.

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The ICH guidelines provide some insights into these conditions. Basically, the ICH guidelines say that a suitable active control must have efficacy that is clearly established and quantified, and where that efficacy in the active comparator trial is similar to what you would have estimated it to be in the historical superiority trials.

Those historical superiority trials could be either add-on trials looking at the standard against the standard plus the experimental, or more frequently, placebo-controlled trials.

[Slide.]

I have reworded this to say these requirements on the active comparator are essentially that the active comparator should be a standard of care intervention whose efficacy is of substantial magnitude that is precisely

estimated where these estimates are relevant to the setting in which the actual non-inferiority trial is going to be conducted. The statisticians at FDA often call the constancy assumption, and I will talk a little bit later about the importance of that assumption.

[Slide.]

Let's illustrate this. Let's say in the context of ABS, where we have a standard antimicrobial intervention, let's say the endpoint is resolution of symptoms at 7 days, and let's suppose that with the placebo, that resolution rate would be 45 percent, and let's say the standard is very effective, it raises that resolution rate to 70 percent.

If that is the case, if I am plotting along this axis where placebo resides relative to the active control, then, what we see is placebo has a 35 percent lower resolution rate at 7 days in the active control.

Now, we don't know that it is exactly 35 percent, it is 35 percent plus or minus the standard errors, and if we had a study with 175 patients per arm, 2 standard errors would be plus or minus 10 percent. Basically, that would mean that the active comparator has anywhere from a 25 to a 45 percent better resolution rate at 7 days.

One approach that has been taken is to then say we will take the conservative estimate of the efficacy and

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argue that the margin is set, so that we preserve at least half of the benefit of the standard antimicrobial.

If we take that approach, then, the margin would be minus 12 1/2 percent, and then when we do our non-inferiority trial to estimate where is the efficacy of this new experimental antimicrobial against that of the standard, the estimate has to be high enough, such that the lower limit of the 95 percent confidence interval rules out that it is 12 1/2 percent worse. That would be one approach.

Now, it might be argued, well, why am I preserving half of a conservative estimate of efficacy, why not take the actual point estimate, and that is where this issue of the constancy assumption comes into play.

I actually don't know what the efficacy of the active comparator is in the non-inferiority trial. I only know what it was in the historical studies.

Well, for example, to take an extreme case, suppose these historical studies were conducted where a large fraction of these or a larger fraction of these infections were bacterial rather than viral, and suppose the assessment was cure rate at 7 days, so that there is a substantial effect of antimicrobial in that setting, but suppose the non-inferiority trial is done in a context where it is much more viral infection and I am looking at

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cure rates at 14 days rather than 7 days where the placebo itself would have a much higher cure rate.

Well, in that setting, we wouldn't have a 35 percent efficacy of the active comparator when we are predominantly looking at viral infections and we are looking at resolution of 14 days, efficacy might be very low.

If we are using a margin of minus 12 percent, when the actual active comparator has a placebo that is very close to zero, we wouldn't even be able to conclude we are better than placebo. So, uncertainties about the validity of this assumption or of this evidence for the effect of the active comparator historically for what it would be, for what the effect would be in the non-inferiority trial is critical and it is one of the reasons for having more caution here.

[Slide.]

The margin here should not only, though, be chosen based on these considerations, they should also be chosen based on clinical relevance issues. If we are saying we can't be meaningfully worse, we need to be thinking about from a clinical perspective how important is it to be somewhat worse, and that should guide the decision about size of margin, as well.

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So, for example, if we have a new antimicrobial that has an improved safety and tolerance profile, easier a administration or allows us to more effectively address resistance issues or drug-drug interaction issues, that might allow us to choose a somewhat larger margin.

On the other hand, if we have a setting where reducing efficacy has a very substantial clinical effect, if it was efficacy and fungal infection or efficacy in HIV transmission, then, that would lead us to choosing a smaller margin.

[Slide.]

All things considered, the ICH guidelines say determination of the margin in a non-inferiority trial needs to be based on both statistical reasoning and clinical judgment issues that I have just been discussing, and should reflect the uncertainties and the evidence on which the choice is based, and therefore should be conservative, one should be cautious about how big a margin one chooses.

One of the additional motivations for this caution comes from the realization that what if I do a non-inferiority trial today for a second generation antimicrobial comparing it to a first generation, and then I do another one several years from now, the third generation against the second, and then a fourth against

the third, where I keep trying to rule out I am meaningfully worse, but I am very lenient in what it means to be meaningfully worse, how many of these do I do before I realize I have a clue no longer about what the actual efficacy is.

[Slide.]

This is not entirely a hypothetical. Two years ago, the Anti-Viral Drugs Advisory Committee was asked to consider Voriconazole as empiric anti-fungal therapy for febrile neutropenic patients. Essentially, their evidence was based on three series of studies: an original study looking at Amphotericin B, then, a second generation study looking at the liposomal version against amphotericin, and then the third generation looking for Voriconazole against Ambisome.

What was the essence of the challenges that the Anti-Viral Committee had to face? Well, first of all, the endpoint here, failure was considered to be either death, fungal infection, breakthrough fungal infections or persistent fever, so success is one minus that.

The amphotericin B evidence was actually based on studies from EORTC and Peizo studies that were more than 25 years old and were based on extremely small sample sizes that basically showed there was a positive trend, but

didn't even achieve statistical significance for evidence of benefit.

The Mycosis Study Group did then the second generation Ambisome against amphotericin comparison and showed similar success rates.

The third generation study, looking at Voriconazole against Ambisome came up with some interesting results from a couple perspectives. First of all, the success rate on Ambisome was 30 percent compared to the 50 percent success rate in the non-inferiority trial that established efficacy of Ambisome, in essence in large part because a different definition of success was used. It used a different duration of persistent fever when defining what was failure.

So, the question is would Ambisome have been adequately effective under that different definition. We don't know the answer.

The other issue is that Voriconazole was actually, by point estimate, 6.5 percent less effective, and with a lower confidence interval indicating it would be as much as 12 percent less effective. So, using a more conservative lower limit as a guideline, the Anti-Viral Drugs Advisory Committee did not approve Voriconazole, believed that these data were not sufficiently reliable.

But suppose it had approved by taking a more lenient criterion here for the margin? Then, if a fourth generation antifungal therapy came along, might you compare it to Voriconazole, and then what margin would you use and at what point would you really know whether or not these therapies are truly causally influencing or positively affecting the success rate.

[Slide.]

What about in acute bacterial sinusitis? I will just be very brief here because I think there will be more discussion of this data later on by FDA. There was a meta-analysis showing that there were 14 placebo-controlled trials of antimicrobials that have been conducted since 1969, interestingly, 9 of these 14, though, just in the last 7 years.

The outcome in these studies were antimicrobial effect on resolution or improvement of symptoms assessed at some fixed day that was some time between 7 and 14 days.

[Slide.]

This plot then shows the antimicrobial efficacy for these studies, and essentially, it looks at the difference in success rates in resolution of symptoms on intervention versus control. Actually, if you are looking at the 16 datapoints, but 2 of these, this one and this one, are actually subgroup analyses, so if you take those

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out and look at the remaining 14, what you see here is that there is some heterogeneity in the efficacy estimates we get against placebo, but two-thirds of these really show rather trivial differences.

There are many issues as to why that may be the case, I won't get into those right now, but the general sense is if this is the type of data that we would have, does this put us in a position that we can justifiably define a margin if we were to use any of these antimicrobials as a standard against which we were going to compare an experimental antimicrobial. How could we define a non-trivial margin? We would need to know that that standard had a substantial level of efficacy that was reliably and precisely estimated.

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So, essentially, following the ICH guidelines, if we are suitably conservative, there are situations where it really wouldn't be possible to justify a non-trivial margin, and, in fact, is that not where we are at least at this point in time in ABS.

If one is in that circumstance, then, certainly it is reasonable to consider placebo-controlled trial as one approach that would be ethical and certainly quite scientifically reliable in assessing the actual efficacy of an experimental antimicrobial.

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[Slide.]

Briefly, the last point I want to turn, the issue that has been raised in our questions that we have to discuss today, which is time to event analyses.

In a self-resolving disease, it is entirely possible if what we are looking at or looking for is resolution of symptoms, we might miss an effect if, for example, we are looking too late in time where, in fact, the control itself has substantially high levels of resolution.

The effect may be that we are actually getting clinically meaningful benefit to patient by resolving those symptoms sooner. So, as is noted in the briefing document, it may be more appropriate to measure time to resolution or improvement of symptoms.

[Slide.]

I just wanted to do a quick calculation to show that this, in fact, is a viable approach. If one was looking at time to resolution of symptoms as the primary endpoint, and one had a 7-day average or 7-day median time to resolution with a placebo, a no-treatment situation, the placebo had 7 days, if an antimicrobial would reduce that to 5 days, it would only take 200 patients per arm to have a very high power to pick up this 2-day reduction, and you would actually achieve statistical significance if your

estimate was only slightly more than 1 day, so it would be a very viable approach to take.

[Slide.]

In summary, certainly there are a number of criteria to consider in choosing endpoints. One of those criteria that is very key is clinical efficacy measures or measures that unequivocally reflect tangible benefit are measures that need to be assessed. We need to understand whether or not the intervention truly is providing improvement to the patient in a tangible way.

Microbiological measures are very important. They tell us about mechanism of action and biologic activity. If we are using those microbiologic measures and we show that bacterial eradication is correlated with resolution of symptoms, that result alone does not allow us to conclude that we actually have a treatment effect on resolution on symptoms.

What we have to be able to show is the antimicrobial's effect on resolution of symptoms is fully mediated or fully captured by the bacterial eradication, and that is much more difficult conclusion to achieve.

Non-inferiority trial designs provide us one approach to assessing efficacy of a new antimicrobial, but to use a non-inferiority trial approach, one needs to have standard of care antimicrobial that has substantial

efficacy that is precisely estimated in a context or in a setting that is relevant to the setting in which we are actually going to be doing the non-inferiority trial.

That is going to be necessary for us to be able to justify a non-trivial margin. In settings where non-trivial margins can't be justified, placebo-controlled trial provide us one alternative in general superiority trials, which placebo-controlled trials are one type of trial, would be alternative approaches, and in self-resolving diseases, in order to avoid missing true benefit, it may be that looking at time to resolution is, in fact, one effective way of getting sensitivity to an important clinical benefit.

DR. LEGGETT: Questions for Dr. Fleming? Don.

DR. PORETZ: Actually, I wanted to ask Dr. Sydnor a question. Can I ask him?

DR. LEGGETT: I think so.

DR. PORETZ: With the benefit of statistical analysis, you have been in practice a long period of time, have a wealth of experience in treating sinusitis. Over the years that you have taken care of patients with sinusitis, the antimicrobics that have been developed have been significant.

Tracing the history of these antimicrobics and the development of third and fourth generation drugs, have

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you, based on your experience, noted a difference in the outcome of patients as these drugs have been developed clinically? Do patients in your experience get better quicker with these newer antimicrobics as compared to years ago?

DR. SYDNOR: Yes, very definitely so. Just based on the fact that we do not have to do lavage many times again in a nonclinical trial study, but to have to wash your sinus at the end of therapy is somewhat unusual now, when it was very, very common back in first generation antibiotics.

DR. PORETZ: What about the other complications, after someone had an episode of acute sinusitis, and those individuals several years ago who did not have access to antimicrobics, and you had to wash their sinuses out, were there other significant complications except for the localized sinus disease?

DR. SYDNOR: Yes. Again, the numbers are fairly rare, but we used to see orbital infection and intracranial complications which are extremely rare now in people that have an acute episode, it is much more common in people with chronic sinusitis.

DR. LEGGETT: Dr. Fleming, we can't really expect antibiotics to make people feel good. The only thing we can clinically, relevantly expect is that they eradicate

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bacteria. Your talk was about self-resolving diseases and coming up with endpoints.

How do we get at this question of rare nonself-resolving disease stuck in the midst of all this multiple of patients with the self-resolving disease in terms of the comments you made?

DR. FLEMING: That is certainly an important question. I am looking at two domains here. One domain is bacterial eradication, which is a key biologic effect, and we are hoping through bacterial eradication that we are going to achieve outcomes which would be tangible to the patient.

So, as a patient, what I would want to have would be resolution of my symptoms, and as you point out, one aspect then of that clinical benefit would be whether I have a higher rate of resolution of my symptoms or shorter time to resolution.

A separate benefit would be, if I am understanding your question, potentially a reduction in the rate of much more serious but much more rare outcomes, and this is a particularly difficult issue because the clinical trials that we would typically do, unless we went to enormous sample sizes, are not going to be powered to be able to show those types of effects.

Can we presume those types of effects? Well, I would ask how do we know, what is the scientific evidence that even if there is a correlation between the existence of those side effects or those long-term effects with ABS, that a certain type of effect on bacterial eradication wouldn't necessarily lead to an effect on those more rare endpoints.

Then, what I would have to say is if the benefit isn't in the largest fraction of people having a discernible improvement in resolution of their symptoms, the benefit is only in these very rare instances, then, I have to say at what price are we paying to achieve those, are there issues of resistance that arises from frequent use of antimicrobials that would also need to be used in other settings, and if we are inducing resistance, the complications and the prices that we are paying could also then be substantial when you are adding all this up.

So, it is certainly a relevant issue, but I would argue that it is not even necessarily clear that bacterial eradication will necessarily influence the rate of those rare outcomes.

DR. LEGGETT: Joan.

DR. HILTON: When Dr. Gwaltney presented criteria for a clinical trial, he included that the patients should be 7 to 10 days into their disease course. It seems like

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if you are evaluating patients at that time point, you might have a pretty good idea of which cases are self-resolving and which ones are not, and you might be able to exclude the less severe cases from the protocol all together.

DR. LEGGETT: Ellen.

DR. WALD: If I just might make a comment to that, I think one of the very important things about distinguishing a child or an adult who has an uncomplicated cold from someone with sinusitis, is that not only are they symptomatic at 7 to 10 days, but they are not improving, so there will be many patients with colds who still have symptoms at 10 days, but they have clearly turned the corner, and those are patients that you really don't want to include in a clinical trial.

I think this concept of time to clinical cure is really extremely important, because as was said, in any self-resolving illness, I think the major benefit that you are going to see is that patients are going to get better faster, as well as hopefully more often, so this is one approach which I think is very important.

One thing I just would worry about is that patients are sometimes loathe to say they are completely well. You know, they will just keep saying they have one persistent residual symptom, so I think one of the things

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that might be important for us is some kind of scoring system, so that we can say that some very modest residual symptom will not count against a patient being considered a cure.

An alternative might be to use as an endpoint something early in the course of disease. What I have done in the past is to do an outcome at 3 days, as well as an outcome, say, at 10 days. But I think if you could do this kind of analysis of time to cure with some kind of a scoring system, it would be extremely valuable.

DR. LEGGETT: John.

DR. BRADLEY: I have got a few comments on overall clinical trial design that we are trying to get around this morning. Obviously, the microbiologic evaluation is critical in the assessment of whether the antibiotics are effective or not, and I think everyone pretty much agrees with that.

Hearing the statistical considerations with bio-creep, which we certainly have gone into in other diseases, and the need for placebo-controlled trials, it brings up the ethics of doing placebo-controlled trials here in the United States.

In terms of my enrolling young children with sinusitis in a placebo-controlled trial, it would be very

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difficult for me to talk any parent into that at this point in time.

However, many of the clinical trials are done in many different countries in the world, sponsored by companies with protocols that go through the FDA, and a trial on the efficacy of pneumococcal conjugate vaccine in the prevention of otitis media was done in Finland where, at birth, it seems that the parents were signed up and randomized and agreed to allow their children to have their ears tapped anytime they subsequently got an ear infection, which is a trial design that would be very difficult to do in the United States.

So, as we struggle with trial design considerations, trying to get the best data to arrive at statistically valid, clinically applicable conclusions, I am wondering how we should put this together, whether it should be just for the United States, the United States plus other countries, or look at perhaps doing some of the trials in other countries where it is ethically acceptable in other countries, but perhaps very difficult to do in the United States.

Many of these companies that have antibiotics are multinational companies with investigators in many different countries.

DR. LEGGETT: Ken.

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DR. BROWN: After listening to these presentations, I have questions about the gold standard issues. It seems that if we have only three products which are licensed for the treatment of acute bacterial sinusitis, and it didn't sound from our speakers that they were necessarily limited to those in their experience, and if the trial designs for those three--is that correct?

DR. ALBRECHT: Actually, we probably have about a dozen. You may be thinking of yesterday's topic.

DR. BROWN: Right. But over the course of the time during which these have been developed, the study designs have not necessarily been the same. If I understood both the statistical issues in Dr. Gwaltney's talk, there have never been any studies which really meet an idea standard for defining this.

So, how do you pick what would be useful legitimately and ethically as a gold standard?

DR. POWERS: I think to sort of answer that, I am going to defer because that is what we are actually going to address. Dr. Pohlman is going to show this afternoon what we have actually been seeing in the clinical trials that have been submitted, and then we are going to try to go on and try to answer that question.

DR. LEGGETT: Janet.

DR. ELASHOFF: With respect to the comment about maybe placebo-controlled trials could be done elsewhere, the issue of whether we could really make valid inferences from that situation to the situation here is a major one, especially if you start to think about the bacteria that might be involved, the percent of patients that might actually have a bacterial infection, other aspects of treatment in a different place, I think one would have to be extremely careful about assuming that results from some other country would apply here.

DR. LEGGETT: Jan

DR. PATTERSON: Well, it seems like a lot of this discussion is very similar to the acute otitis media discussions that we have had before, and some of the things that came up in that were that pneumococcal otitis media was easy to distinguish and was more severe than other bacterial types of acute otitis media which looked very similar to viral otitis and you couldn't really distinguish them without a tap.

So, you might could justify a placebo-controlled trial for acute otitis media for other than pneumococcal presentations. But it seems to me, based on the information that Dr. Gwaltney gave us, that there is enough criteria to distinguish bacterial sinusitis from viral

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sinusitis, you know, make a placebo-controlled trial not really necessary in this instance.

The concern I would have about encouraging other countries to do it if we are not willing to do it is, first of all, to me kind of an ethical concern, but also I think that in other countries, there would be different risk factors and maybe even different epidemiology of pathogens, different resistance patterns, and so forth.

DR. LEGGETT: Alan Cross.

DR. CROSS: I have a question for either Dr. Fleming or John Powers. We have talked about the time to event. Is it sufficient simply to show a statistically significant difference, or if not, what considerations ought we have?

For example, I am thinking of the neuraminidase inhibitors which are approved here, but when evaluated in the UK, my understanding was that even though there was a difference, it was not sufficient for them to actually approve the drug.

DR. LEGGETT: Tom.

DR. FLEMING: Let me begin at least, then, Dr. Powers may have something to add.

In thinking through the design of trials--and I think Dr. Cross is raising a very key point--I would start at the point of trying to identify what is really the most

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clinically relevant outcome that patients would want to achieve.

Let's suppose we arrive at resolution of symptoms. In a self-resolving disease, in order to not miss a clinically meaningful effect, if we decide to go with trying to show we have a shorter time to resolution, I see that as being very relevant.

Your point is well taken, though. You do need to see more than just a statistically significant change. That has to be judged to also be clinically meaningful. So, a one hour shortening is not clinically meaningful. So, what one has to arrive at in the design is what level of improvement on this clinically important endpoint will be clinically meaningful - is it a day, is it two days.

Then, one needs to design the trial to be adequately powered for that clinically meaningful change. But you are absolutely right, it has to be ultimately an outcome that is simultaneously clinically important, as well as statistically established.

DR. POWERS: I agree and I think the other thing Dr. Cross brings up is that it also depends upon that decrease in the time that you have symptoms, it may also be relevant as to when that decrease occurs. As a clinician, I would think a decrease from four days of symptoms to

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three days of symptoms, similar to what we saw with neuraminidase inhibitors.

It would be a lot different if it went from 12 days to 11 days, even though it is the same absolute decrease, because if you are sick for a week and a half anyway, what difference does it make, as opposed to taking a short disease and making it shorter.

So, I think one of the questions we are going to ask you today, and I am going to show exactly a slide about neuraminidase inhibitors and relate these two to each other, is what would you folks consider a clinically meaningful difference in this disease.

DR. FLEMING: Just to add one additional thought to that, if you were reducing from 4 to 3, that is a 25 percent relative reduction. I had given the example of 7 to 5, which is almost exactly that same relative reduction.

DR. LEGGETT: Any other questions, comments?

We are only running 10 minutes late today. That is good, an improvement.

Why don't we come back in 15 minutes.

[Break.

DR. LEGGETT: I would like to ask Dr. Powers to respond to Dr. Bradley's query about doing placebo-controlled trials overseas.

DR. POWERS: I sort of want to make a more general comment about doing trials overseas, period.

First, a couple comments. One, we have been saying data in this disease and in others from overseas. The only thing that the Code of Federal Regulations says is that those diseases have to be similar to diseases that would occur in the United States.

The data that we have seen shows this disease is very similar, and the degree of organisms that occur in the disease are very similar, as well, so we could do trials overseas and they would be acceptable.

DR. LEGGETT: Thank you.

The next speaker is Dr. Kraus, who will talk to us about Clinical Evaluation of Acute Bacterial Sinusitis and Diagnostic Considerations.

Clinical Evaluation of ABS:

Diagnostic Considerations

DR. KRAUS: Thank you.

As Dr. Albrecht mentioned earlier today, the overriding goal will be to try and provide some literature context on the diagnostic criteria used for acute bacterial sinusitis and how that might relate to clinical trials inclusion criteria.

[Slide.]

Specifically, as Dr. Gwaltney has already mentioned, the percentage of patients that have sinusitis are exceedingly rare with a bacterial etiology based on the two studies that he presented, and the question I am going to try and address is how do we better hone on that individual that actually has bacterial sinusitis.

[Slide.]

One might hypothesize that there are a constellation of symptoms and imaging techniques that, when overlaid with cultured-proof punctures, would better populate the inclusion of patients with acute bacterial sinusitis in clinical trials.

I guess the overriding question I am going to try and directly address is what evidence is currently present in the literature that correlates these specific diagnostic criteria for individuals that have acute bacterial sinusitis.

[Slide.]

The methodology that I am going to describe is going to be related to these four key elements that I used in looking at the literature, specifically, whether or not symptom duration actually is addressed in the literature as to what percentage of patients develop or have bacteria etiologies, whether there are specific symptom characteristics that best describe patients with bacterial

sinusitis, or that there are radiographic criteria that can also delineate patients with bacterial sinusitis, and finally, I will also describe the two studies with regard to endoscopy that has been addressed at advisory committee meetings before this one.

[Slide.]

Specifically, the search strategy I used in looking at the literature was seeking those studies that specified inclusion criteria and had a sinus puncture with culture as part of the initial evaluation.

Now, many of these studies that I looked at weren't specifically geared at trying to define these populations, but had embedded data that I pulled out, and many studies in the literature regrettably have many sinus punctures, but only have qualitative data describing purulence or non-purulence.

There is a paucity of studies that actually have bacterial cultures performed at the same time. I think it is important to make that distinction because there is a handful of studies showing that even non-purulent disease have a large proportion of bacterial etiologies.

Other line items that are worth noting here, that I looked at in the literature, were the type of study populations looked at in these various studies, the use of

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microbiologic cutoffs, and the specified inclusion criteria.

[Slide.]

The general methodology was to do medical subject headings search in the Medline database from 1966 to present, superimposed with that keyword searches for the specific disease entity, looked at the article references, evaluated the abstracts, and then did full article reviews for those that were thought to be relevant.

[Slide.]

Ultimately, what I found was no studies that could specifically describe symptom duration as how it correlates to acute bacterial sinusitis. There were 5 studies that described some symptom characteristics and how they related to culture-positive rates. There were 12 that I identified with radiography-included data, and there were 2 studies that I will discuss with regards to endoscopy.

[Slide.]

Initially, when it comes to symptom duration, Dr. Gwaltney went into this with some detail and I won't belabor the point, so suffice as to say that in patients with disease that has lasted for only 7 days or so, as you go out in the disease process, it is less likely that you are going to have a viral etiology for your process.

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I don't know what that is really going to say about bacterial etiologies, but you can probably guarantee that the risk of a viral etiology is diminished after 7 to 10 days.

There was a comment in one article by Lindbaek, I think it was in Hickner's article, that stated that bacterial sinusitis is seen in only 20 percent of patients with symptoms less than 7 days although data wasn't provided with that citation.

[Slide.]

With regard to symptom characteristics, I want to underscore the point that much of what I am describing here is in some ways comparing apples with oranges, because the reporting that is described in many of these articles is disparate.

[Slide.]

What do I mean by that? I mean that patient-based reporting--and I have just created an example here to sort of describe this a bit--if one were to look at an article that had 30 patients included, and 15 of those patients had at least 1 sinus that was considered to be positive, we would say that it has a 50 percent positive culture rate.

However, if you took 30 patients on a similar study and reported it, instead of based on patient data, on

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sinus data, such that there were 60 maxillary sinuses that were potentially tapped, 40 were positive, you would say there was a 67 percent positive culture rate.

Lastly, there are some studies that describe their database on aspirates, such that again you might culture more than even the 2 aspirates from those 2 sinuses, such that you might have a higher or a lower culture rate depending on the type of reporting that was included just to underscore the fact that much of this data is disparate and must be taken with a grain of caution.

[Slide.]

So, what I have done in this initial slide is to pull or describe those five initial studies that tried relating symptom characteristics to positive culture data. I think the important thing to note here is that at the top of this slide, the positive sinus culture rate I have noted here is 34, 60, and 65 percent for the initial three studies I have remarked on.

The initial studies that is in italics, 34 percent, I made it italic and I put it in italics because a large section of those patients, I think it was 40 patients actually, had radiographic data, as well, so it somewhat dilutes the study.

The study 2 and 3, that really only had symptomatic criteria at the time of inclusion were somewhat

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pure in that sense, and down the lefthand column you can see that in the second study, only headache, purulence, and facial pain were needed for inclusion, which allowed a 2-fold increase sinus culture rate compared to the first study, with the inclusion of purulence and facial pain.

In Savolainen's study, which is No. 3, he required 2 of any of these data for inclusion in the study, implying that perhaps with an increase in study inclusion, there is a modest increase in the amount of positive tap rate.

I included Study 4, which is Berg's study, here because he states an 87 percent positive culture rate, but regretfully, when reviewing the article, there is no specific signs or symptoms denoted in the actual article.

The other article that is quoted frequently at the same time period, from '88, from Berg, only describes purulence versus non-purulence. It doesn't specifically describe positive culture rate data.

So, these are 4 of the 5 that I am remarking on.

[Slide.]

The fifth one identified was Evans' article in 1975, and specific signs and symptoms were not provided in the study, but he does quote that, "Quality, radiation, intensity of facial pain, purulence of nasal discharge or

presence of fever did not accurately predict the presence of infection as determined by aspiration."

So, regretfully, there is no data to actually describe, but qualitatively, he at least describes that there is no direct correlation.

[Slide.]

Underscoring these three studies, as well, are some deficiencies in the three studies that I just outlined. There were no maximum symptom durations in Van Buchem's, as well as no minimum symptom duration. There was no exclusion secondary to antibiotic use, and it was based on patient-reported data as opposed to Hamory's, which was a sinus-based reporting of data.

Savolainen's, which had the 65 percent correlation rate also had 18 percent attrition, such that we don't know what happened to those patients, adding some element of doubt to the study.

[Slide.]

With regards to radiography and how that might impact the positive culture rate in patients that would be included for a clinical trial, there were 12 studies that were identified in the literature.

[Slide.]

I can say that the percentage of subjects with positive sinus puncture ranged quite broadly, from 30 to 77

percent, and there was an extreme heterogeneity of clinical inclusions used in these studies.

[Slide.]

For ease of reporting, I have divided them up into three groups. The first group, which showed a positive sinus culture of 30 to 54 percent, had disparate reporting as well as inclusion criteria. As I have already stated, there is a difference between sinus-based reporting and patient-based reporting. There were two of each in these studies, three of which were adult, one which was pediatric.

In broad strokes, there was a deficiency in antibiotic exclusion for these studies. There were many patients with confounding illnesses in these studies, such as allergic rhinitis and previous histories of sinus surgeries, as well as chronic sinusitis, and there was again no duration cutoff of the 7 to 10 days that was discussed earlier.

[Slide.]

In the second group of patients that were identified based on radiographic and clinical data, there was a positive sinus culture rate of 60 to 66 percent. Reporting again was disparate. There were three studies that were identified, all of which were adult. Three of them were sinus-based reporting.

In one of the studies there was actually both types of reporting stated, and that was Camacho's study. What is interesting there, just to underscore the differences in yield, I think it was 62 percent of sinuses showed a positive culture rate, but only 24 percent of patients. So, depending on how you look at the data will markedly change how you can draw conclusions from many of these studies.

Again, we have a slight heightening of inclusion criteria where now facial pain is part of the inclusion criteria. There are antibiotic exclusions noted in the methodologies, as well as purulence, but again no duration cutoff. I think it is worthwhile to make the distinction between the first three studies and these in that we have something of a heightened inclusion standard for the study evaluation.

[Slide.]

In the third group of studies evaluated, there were three, two of which were pediatric, and two were patient-based reported and one was sinus-based reported. The inclusion criteria were a bit more rigorous with some heightened radiographic criteria, certainly use of antimicrobial exclusion. There was use of microbiologic cutoffs, and there was a duration cutoff in one subgroup of one of the studies.

As you can see, this group at least had a positive sinus culture rate in the 70s.

[Slide.]

I also think it is worth noting that there may be some benefit in specific types of abnormalities noted in radiography and how they may be related to positive culture rates.

In Hamory and Gwaltney's study in '79, it certainly looked like in those patients with positive cultures, if you try and heighten the inclusion criteria with radiographic criteria ranging from mucosal thickening to air fluid levels, you tend to enhance the number of sinuses with positive microbiologic findings.

[Slide.]

In looking at the literature, I could only find one study that seemed to have some evidence correlating CT findings with microbiologic data, and that was Hansen's study. The requirement for study entry was clinical impression.

There were 174 subjects that completed this study 122 were found to have abnormal CT scans of the sinuses at 70 percent, and they had a definition for acute sinusitis by CT criteria, which was mucosal thickening and fluid in the sinus. Ninety-two subjects met criteria for that, and

61 were found to have pathogenic bacteria or 66 percent of these sinusitis-defined CT scans.

I think it is worth noting here that if you use a denominator of all patients that were included in the study, 35 percent of patients enrolled had positive pathogenic bacteria, but now if you superimpose the filter of a positive CT scan, you can double the positive findings to 66 percent.

[Slide.]

Lastly, endoscopy.

[Slide.]

Endoscopy has been addressed in this advisory committee before, I believe.

[Slide.]

There were two studies that I found in recent literature addressing this issue, Vogan and Talbot study. The Vogan study is exceedingly small, 13 patients with 16 sinuses that are addressed in his conclusions.

Thirteen sinuses had previous antimicrobial use. Diagnostic criteria for acute sinusitis was not stated in the article. Only patients with their fluid level, on radiography, were included, and no dilution was noted on semiquantitative microbiology, such that any colony that was counted on the zero plating would be counted as a positive as opposed to Talbot's study which was very well

described with positive minimum symptom durations, positive antimicrobial exclusion, positive chronic sinusitis exclusion, positive dilutions noted on semiquantitative microbiology with specific radiologic findings noted.

[Slide.]

If we look at the two studies in tandem, what you see is that with Vogan's study, there was a sinus puncture that was found to be positive, 14 of 16 sinuses, but if you used more stringent criteria of what constituted positive microbiologic findings from 1+ denoting just a few bacteria, that you would only have 4 of 16 sinuses positive if you were raising the bar above 1+.

So, overall, 8 of 14 sinuses was positive ipsilateral endoscopy, had sinus puncture with the same pathogen.

In Talbot's study, which was a very well defined patient population, there were 31 of 46 patients with positive endoscopy, and overall, 12 of 31 patients with positive endoscopy had sinus puncture. I think it is important to remark here that on the left, we are talking about sinuses, and on the right we are talking about patients, and that is something else that I think is not well standardized and hard to really compare in the literature.

[Slide.]

So, overall, the initial question, the specific question I tried addressing was does the literature adequately describe specific criteria for diagnosis of acute bacterial sinusitis, and I would have to say that with regards to symptom duration, there are no studies identified, but based on Gwaltney's initial data and the data you heard him describe earlier, that there is a high likelihood that you are not going to get viral dilution if you exclude patients who have had symptoms for less than 7 days.

With regards to symptom character, there were 5 studies identified, 2 of which had reasonable data with inclusion symptoms and signs, which gave you a 60, 65 percent positive culture rate.

Radiographically, there was a broad range of studies comparing sinuses and patient-based reporting in their methods, and there was a broad range of inclusion criteria with positive culture rates ranging from 30 to 77 percent, and finally, with endoscopy, there is only the two recent studies that I just reviewed with positive results ranging from 30 to 57 percent, but again, sinuses versus patients.

[Slide.]

So, overall, I think we can say that symptoms are certainly necessary, but not sufficient for bacterial sinus

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diagnosis for the diagnosis in a clinical trial.

Radiography is not necessary or sufficient, but may indeed help enrich a population for acute bacterial sinusitis as we saw with Hansen's study and certainly with the other studies and radiography data.

Given symptoms, cultures are sufficient and since there is no validated or reproducible or standardized surrogate in the literature--when I say "standardized," I mean how do you report the findings whether they be based on sinuses, on patients, or on aspirates--it is currently necessary for the specific diagnosis of bacterial sinusitis for clinical trials inclusion.

Thank you.

DR. LEGGETT: Thank you. Are there any questions for Dr. Kraus?

[No response.]

DR. LEGGETT: Thank you very much.

Dr. Pohlman is now going to address us with Lessons Learned from Clinical Trial Design and Past Approvals.

Observations from Past Approvals

for Acute Bacterial Sinusitis

DR. POHLMAN: Actually, I think my titles of my talk in the agenda keep getting switched, and I think this was the first title before I switched it three times.

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Anyway, what I am going to talk about today is the observations that have been made from past approvals for acute bacterial sinusitis, my observations actually.

[Slide.]

What I am going to do today is talk a little bit. Dr. Albrecht actually went into detail about regulatory guidance that we give to industry in the form of our 1992 Point to Consider document, and the more recent 1998 guidance document. Basically, the 1998 guidance document is similar to the 1992. It maybe clarifies the language a little bit, but essentially, the points in the documents are similar.

Then, what I did was a retrospective review of drug approvals of which there are 10 for acute bacterial sinusitis since 1990. The purpose of doing this is to sort of let everybody know what we are seeing from industry and in what we are processing in our reviews, and then hopefully to use the information obtained from this along with the discussion today and information that we may have learned to try to see if we need to revise those guidance documents.

[Slide.]

I am just going to go back to try to outline--at the present time, two separate studies are done. The first study is what we refer to oftentimes as the "clinical only"

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study, statistically adequate and well-controlled, multicenter comparative trial where we want to use rigorous case definitions with specific clinical or radiographic entry criteria and where we also try to use rigorous clinical and radiographic endpoints as primary effectiveness parameters.

Sinus puncture in these studies is not necessary, but is encourage in therapeutic failures.

[Slide.]

The second study that we asked people to do, often referred to as the "micro" study, or Dr. Albrecht referred to this as "microbiologically driven" study.

It utilizes sort of the same inclusion criteria from a clinical and radiographic standpoint, but also requires sinus puncture at entry, and that is utilized in the diagnostic criteria of acute bacterial sinusitis.

The purpose of this to establish successful microbiologic, clinical, and radiographic outcomes in at least 100 patients. Then, we come up with the numbers of 25 cases of *Streptococcus pneumoniae*, 25 cases of *Hemophilus influenzae*, 15 of *Moraxella catarrhalis*.

Again, in these studies, post-therapy sinus puncture is strongly encourage in therapeutic failures. Although the overall diagnostic strategy look at microbiologic diagnosis along with the clinical and

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radiographic criteria, the guidance document actually states that outcomes on all patients should be reported even those without pathogens at entry.

[Slide.]

Just a couple caveats in going through this. Basically, the guidance documents are established to serve as a guidance to industry. They are not absolute requirements. It is basically to try to level the playing field for everybody. The fact that the antibacterial agents are reviewed across two divisions, the fluoroquinolones being in the Division of Special Pathogens, and other antibacterials in the Division of Anti-Infective Drug Products.

Another thing is that submissions for acute bacterial sinusitis are generally part of an NDA package and that there may be other respiratory indications that can be used in somewhat supportive fashion.

This last point is important. I decided that this retrospective review of the work of others is equivalent to a chart review or put in something that Dr. Reller could relate to, sending his Clinical Micro fellows around to decide whether the Staph aureus that popped up in the blood culture bottle of the month is truly a true bacteremia.

But at any rate, in a retrospective review, I can't tell whether the data was submitted in the NDA and the reviewer did not choose to focus on it, so nobody gets a grade, there isn't attribution for who is leaving out what, so we will proceed with that understanding.

[Slide.]

What I am going to try to do is go through with the particular language of the guidance document and then kind of take apart each of the particular criteria and look at what I found in my review.

In terms of the guidance document for inclusion criteria, and these actually apply to both the clinical and micro studies, although they are separates studies, these inclusion criteria are pretty much consistent for both of them.

The patient should have a clinical diagnosis of acute bacterial sinusitis based on history, physical exam, and radiographs. The diagnosis of acute sinusitis requires signs and symptoms or recommended signs and symptoms lasting for greater than 7 days.

The signs and symptoms should include facial pain or pressure, purulent nasal discharge, nasal congestion, and cough.

The radiographic documentation should include CT, sinus x-rays, or ultrasound and included comments about opacity, air fluid levels, or mucosal thickening.

[Slide.]

What I am going to do here, as I said, there were 10 drug approvals. Basically, if you say that there is two studies for each drug, that means one clinical-only trial and one micro trial. In some instances and in most cases, it happens in the microbiology arm because of the requirement for number of pathogens that have been considered, multiple trials may be done, but this is going go focus on the clinical-only trial, so we are looking at essentially 10 drug approvals.

The first thing is focusing on signs and symptoms should include facial pain or pressure, purulent nasal discharge, nasal congestion, and cough.

In kind of looking at sinus pain and purulent nasal discharge, it is perhaps major signs and symptoms in the definition. Both sinus pain and purulent discharge were required in 6 out of the 10 NDAs.

One NDA required one or both of these signs to be present or symptoms, and two additional NDAs had listed sinus pain and purulent nasal discharge in a multiple symptom list. Basically, you pick two symptoms out of

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list, and other things could be nasal congestion, cough, headache, fever I guess was in there.

In one NDA, purulent nasal discharge was not required to be included.

[Slide.]

Again, focusing on the clinical-only trials, in terms of the diagnosis of acute sinusitis where signs and symptoms have persisted for greater than 7 days, in 8 out of the 10 NDAs, there is actually no reported minimum duration of symptoms.

One NDA did require 7 days minimum, and a second NDA required a 10-day minimum.

[Slide.]

Again, in the clinical-only trials, the radiographic documentation should CT, sinus x-rays or ultrasound and include comments about opacity, air fluid levels, or mucosal thickening.

I would say the use of x-rays is pretty much universal in acute bacterial sinusitis, and it was in these applications. Use of opacity and air fluid levels was universal, as was use of mucosal thickening, but the extent varied among the NDAs.

Six out of 10 NDAs used anywhere from 4 to 6 millimeters of mucosal thickening, and the extent wasn't reported in 4 out of 10 NDAs.

[Slide.]

So, to move away from inclusion criteria for right now, in terms of efficacy, what we are using as a clinical outcome definition. The guidance document definitions are that clinical cure should be resolution of signs and symptoms at test-of-cure visit and at least no worsening in radiographic appearance, clinical failure, persistence of one or more signs and symptoms of sinusitis or patients receive additional or new antibiotics.

Then, there is an indeterminate category if people don't come back for follow-up, if they get an antibiotic for some other reason, but basically, the guidance document looks at the endpoint as a dichotomous endpoint.

[Slide.]

What are we seeing in the clinical-only trials? In terms of clinical cure defined in the guidance document as resolution of signs and symptoms at test-of-cure visit, 8 out of the 10 actually defined clinical cure as success, and I think this is getting at something Dr. Wald was indicating about earlier, where success actually incorporates categories of cure and improvement, where cure implies resolution of all signs and symptoms.

Improvement, there are varying definitions for that. It is either all signs and symptoms at least

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improved or partial resolution. It is kind of a fuzzy zone.

In terms of the use of radiographs in clinical outcome determination, the guidance document states that at least no worsening in radiographic appearance has to be present for a clinical cure.

Five out of 10 NDAs explicitly used test-of-cure radiographic in the sponsor outcome definition, however, the medical reviewer generally discounted it as sort of lagging behind clinical progress.

[Slide.]

Turning to efficacy, another thing that has been discussed here is in terms of timing of test of cure. Outlined in the guidance document are the study visits that are necessary, and basically, there is a baseline or entry study visit, usually, an on-therapy visit which occurs about 2 to 5 days, an end-of-therapy visit which is an evaluation of patients near the completion of therapy, primarily to optimize patient care, and usually, these will occur anywhere from 24 to 72 hours after therapy is completed.

The guidance document says this visit should not be considered a test of cure.

Then, there is the fourth visit that is outlined is this post-therapy, test-of-cure visit. The timeline for

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this, the guidance document says it should occur approximately 1 to 2 weeks after completion of therapy. This assumes a treatment duration for acute bacterial sinusitis that ranges from 10 to 14 days, therefore, the test-of-cure visit would approximate timing of the 3-week natural history resolution of acute bacterial sinusitis symptoms.

At the post-therapy visit, notes made of results of clinical evaluation, including status of presenting signs and symptoms, as well as radiograph, but that is often discounted.

[Slide.]

In looking through the 10 drug approvals, in terms of timing of test of cure, when are they actually occurring, the actual outcome determinations, the sponsors used the end-of-therapy visit, the visit that is occurring 24 to 72 hours for test of cure determination in 5 to 10 of the NDAs, and the post-therapy or later, 1 to 2 week post therapy follow-up in 5 out of 10 NDAs.

The medical officers use the end-of-therapy visit for test of care determination in 2 out of 10 NDAs, and post-therapy visit in 7 out of 10 NDAs. Usually, there is a primary and a secondary endpoint, so I wouldn't say that they are not looked at, but the sponsors tended to use that early end of therapy determination, and the medical

officers tended to concentrate on the later follow-up period.

[Slide.]

So, now, I want to turn a little bit away from the clinical-only trials and discuss in particular the microbiologic trials, and remember they have the same inclusion criteria that have been previously mentioned for the clinical-only trials, the same efficacy determinations and timing of test of cure.

Indicated in the guidance document, the microbiologic dose diagnosis is based on isolation of a bacterial pathogen from baseline maxillary sinus punctures combined with the clinical and radiographic features.

Documentation should include Gram stain with white blood cell and bacterial morphotype semiquantitation and quantitative bacterial cultures with susceptibility testing.

For pathogen definitions, *Streptococcus pneumoniae*, *Hemophilus Influenzae*, and *Moraxella catarrhalis* are considered pathogens regardless of colony count. *Staph aureus* is considered a pathogen when isolated in pure culture with colony counts greater than or equal to 10^4 colony-forming units per ml.

[Slide.]

So, now when we look at the microbiology trials in terms of pathogen definitions, what do we see? In terms of the major respiratory pathogens, Strep pneumo, Hemophilus Influenzae, and Moraxella catarrhalis, 6 out of 10 NDAs considered these organisms pathogens regardless of colony count.

Three out of 10 NDAs had no reported definition of pathogen, and what I mean by this is that they could have included coagulation-negative staph as a pathogen. There was no particular list to get around or there may have some individuals with gram-negative rods that were in the aspirates, and they were considered to a pathogen.

One NDA required quantity of greater than or equal to 10^3 colony-forming units per ml for the major respiratory pathogens.

[Slide.]

In terms of Staph aureus, 8 out of 10 NDAs considered Staph aureus as a pathogen and were pursuing Staph aureus in their labels. Only 3 of these applied Gram stain or quantitative measures to assess the presence of Staph aureus as a pathogen, however, information was available for the medical officer to apply Gram stain or quantitative requirements to Staph aureus pathogen definition, and 2 out of those 5 NDAs didn't have that information utilized by the sponsor.

[Slide.]

Then, in terms of trying to talk about sinus puncture yields in our micro-only trials, this was a tough thing to get around. As Dr. Kraus indicated, the level of positivity of aspirates can vary depending on the reporting.

The sinus puncture cultures were positive in 22 to 87.5 percent of patients enrolled in the microbiology clinical trials. I would say that is a wide range.

However, the reasons for the rate of positivity are perhaps a little different than what Dr. Kraus indicated earlier. They seemed to be influenced and the analysis complicated by what the pathogen definition is. NDAs with pathogen definition, companies that were just looking for the major respiratory pathogens and maybe discounted other ones tended to focus on those as their positive aspirates.

So, those where there was a pathogen definition, we had aspirate positivity rate or puncture positivity rate of 36 to 55 percent of the patients given the inclusion criteria that we had.

NDAs with no recorded pathogen definition, meaning anything could be a pathogen, were positive in 66 to 72 percent of patients, and then there were actually 2 out of the 10 NDAs where puncture positivity rates appeared

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to be low, 22 percent and 42 percent, but they were likely underestimated by presentation as the microbiologically evaluable patients.

Basically what happens is that you take your clinically evaluable patients, you know, people that have gotten drug for long enough and people that have had appropriate follow-up, and then you separate out the people that had a pathogen isolated on the baseline sinus aspirate, that's your population, your denominator, but people can be eliminated from the numerator for other reasons besides culture positivity. Perhaps they didn't have their follow-up visit, there is other reasons to take them out of the denominator.

[Slide.]

In terms of bacteriologic efficacy, how do we address that? In the approved NDAs, the majority of bacteriologic outcome determinations are extrapolated from clinical response. This was seen in 9 out of 10 NDAs.

There was a single NDA with relatively complete post-treatment follow-up sinus puncture. Sinus puncture is rarely done in cases of clinical failure. There was information in 4 out of 10 NDAs where there were some sinus punctures done, but it is not a consistent finding.

[Slide.]

I guess in summary, I just wanted to sort of restate the fact that at the present time we have the two separate trial. The micro trial utilizes the microbiologic data from the sinus puncture in addition to the clinical notification in the diagnosis of acute bacterial sinusitis.

Although the clinical-only and micro studies are not directly linked, the inclusion criteria for both are often similar in the applications we receive.

The rates of sinus puncture positivity varied widely, from 22 to 87.5 percent, and are dependent upon the pathogen definition, method of collection. Although we require sinus puncture, there were a few studies where there were some endoscopy patients thrown in and sort of analyzed separately, but the method of collection as stated in the guidance document is the sinus puncture, and sinus culture positivity also varied depending on the population being reported on.

[Slide.]

My last little point, and I think Dr. Gwaltney touched on this a little bit earlier, although at the present time, x-rays are recommended at the end of therapy to document clinical cure, they are seldom used especially by the FDA as a basis for determining efficacy, recognizing that they may lag behind the clinical course.

DR. LEGGETT: Any questions? Don.
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DR. PORETZ: Obviously, the microbiological data is critical. The laboratories used, I am sure varied all over the lot. I know studies that we have done in the past require different laboratories. Third-party payers are contracted to different laboratories. Transport may take hours and days before they are looked at.

What is your experience in reviewing the microbiology laboratories that have participated in these studies?

DR. POHLMAN: I am going to turf that to someone else. Actually, in my review, I didn't focus on what the mechanism for obtaining cultures was. Oftentimes the cultures may be done locally and then confirmed at a reference lab that is part of the study protocol.

I will let Dr. Albrecht comment.

DR. ALBRECHT: That is what I was going to say. We basically just specify in the protocol what are the parameters and criteria for diagnosis, and actually I don't know if our Microbiology staff may want to further elaborate on the protocol definitions, but then the sponsor actually makes the selections of the laboratories, both the local and the central, and follow their QC procedures. We don't actually go out and look at those laboratories.

DR. LEGGETT: If you could address that issue.

DR. SILVER: Harold Silver, Microbiology, Anti-Infectives. The microbiologists, what we do is we compare the methodology and all the information that is sent to us by the applicant or sponsor, to standardized methods and other information, and we compare it to what standardized out in the community.

So, we do compare everything, and if there is a discrepancy, we mention it to the applicant or sponsor, but we ensure that the specimens, and so on, are guided by standardized methods and guidelines that are out there.

DR. LEGGETT: Thank you.

DR. TUNKEL: In terms of the two studies, the clinical-only and the micro, I guess in terms of specific antimicrobial agents studied, was the clinical cure the same in each study? That is, when you compared clinical to micro, did really your success rate make a difference in doing both studies?

DR. POHLMAN: I would say they were not necessarily the same. I think Dr. Albrecht indicated earlier, too, about the fact that oftentimes the microbiology trials are non-comparative trials, they are not blinded. Cure rates could be higher, I don't want to generalize. There were about 30 studies that I looked at, so there is not a real good way to generalize that comment.

DR. LEGGETT: Dr. Wald.

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DR. WALD: The idea of setting a specific colony count in the quantitative data is to try to ensure that pathogens that are recovered represent infection of the maxillary sinus, and not the nose, so I was a little surprised to hear that you take any colony count for Hemophilus influenzae, Strep pneumoniae, and Moraxella catarrhalis.

Even though I know those are not regarded as normal nasal flora adults, when an adult has a cold, I would just wonder if you couldn't find those organisms in the nose, and if you wouldn't do better to ensure the validity of the culture representing again maxillary sinus disease rather than nasal colonization.

In children, it is absolutely true that these are normal nasal flora, so for childhood studies, quantitation really would be essential. This was the same issue that we deal with in urinary tract infections. You know, we know the distal urethra is colonized, so we set our definitions of significant bacteria accordingly. I think for children, we absolutely have to do that.

DR. ALBRECHT: I would say that I shared your surprise when I read the document again this time in preparation for this meeting, and as I mentioned in the introduction, I think this was really, again, we, as a regulatory agency, have parameters and criteria that we try

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to provide in our draft or finalized guidance documents, but we often hear concerns raised by companies about why that may or may not cause difficulties in enrollment.

I think as I reflect back on sort of this work of a committee of experts internally and advisers from external sources, is that I think what must have happened, as we were considering this, we realized that in addition to having an aspirate with Gram stain predominant organisms, white cells, et cetera, that occasionally, the only that was quote "wrong" was that the colony count, it perhaps was not done, but in the setting where all the parameters were there including white cells and the predominant morphology of an organism on Gram's stain, so perhaps in the spirit of trying to be more inclusive instead of exclusive, we proposed that quantitation for the main three organisms not be mandated or not be really focused on completely.

But I share your observation.

DR. LEGGETT: Dr. Gwaltney.

DR. GWALTNEY: As I understood those data, Ellen, those specimens were sinus aspirates, they were not nasal, they were sinus aspirates.

DR. WALD: They are saying any positive culture from a sinus aspirate--

DR. GWALTNEY: From a sinus aspirate, yes.

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DR. WALD: --equals a positive culture. You certainly didn't say that in your studies. You required 10^3 .

DR. GWALTNEY: In our original, but I mean I think you can make the argument, which I tend to believe, is that the sinus clearly is sterile under normal conditions like bloodstream, the bladder, CSF, so that in this setting, if you do get any organisms of those three in that sinus aspirate culture, I have no trouble believing that they probably did come from the sinus cavity and you just caught the patient early in the infection, although you can never rule out the possibility that they might have been contaminants, but that more likely of proper care was taken in collecting the specimen, that they really do represent the fact that those bugs are in the sinus cavity.

So, I don't see any problem with that. I would think that is the appropriate way to do it.

DR. WALD: I would just worry about contamination. I think people are not always so careful and that nasal cultures can often be positive.

DR. LEGGETT: Dr. Pohlman, did you see or does the FDA keep track of any adjunctive therapy?

DR. POHLMAN: Adjunctive therapy, that is an interesting point because I think--and I can't generalize

because I didn't really pick that out for each of these particular categories.

What I would say is that there are some that allow adjunctive therapies, decongestants, some that don't.

DR. LEGGETT: Dr. Gwaltney, what would you say about the effect of any adjunctive therapy on resolution rates if we are going to be talking about floating end periods of resolution of symptoms?

DR. GWALTNEY: Well, again, we have no data to start with. I think decongestant therapy theoretically makes sense, but I don't think it probably influences the outcome very much, and when you talk about things like steam, it is so difficult to get anything into the sinus cavity, because it is so sheltered behind the infundibulum and the inferior turbinate, and then you have got that tiny little opening with the angle, and it is hard to get steam or anything else in there.

Then, on top of that, it is usually occluded with material, so I think we fool ourselves really when we think putting all this stuff up the nose is going to do much to sinus. It may help the middle meatus. I think that is what the decongestants do is they shrink that area.

It would be nice to have randomized in terms of the adjunct therapy, but personally, I don't think that is a big issue.

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DR. LEGGETT: Dr. Reller.

DR. RELLER: There is not as big a discrepancy here between the quantitative cultures and any organisms as might appear on the surface, because in reality, to get any organisms requires something about 10^3 or more given the small sample size that is actually plated.

There are published reports of what sounds very crude in terms of quantitation, but a properly streaked plate, you know, what grows in the first, second, third, fourth zones correlates actually quite well with 10^3 , 10^4 , 10^5 , 10^6 , and then if one couples, which I think should always be done, I think a culture should never be interpreted without a Gram stain of an aspirate or sputum specimen as far as that goes, because they are complementary and serve as a quality check each on the other.

So, if one sees the organisms that are consistent with a Pneumococcus or Hemophilus influenzae, and then you grow, even it's only 1, 2, 3, 5 colonies, you have got a good case, and that is especially true in sputum samples.

I mean anybody that would do a sputum culture without a Gram stain smear, I think is kidding oneself. So, I think they are complementary and I would like to see that, and, in fact, if one sees, to the extent that this material is liquid or semi-liquid, to see one organism per

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high-powered field, you are up in the 10^4 , 10^5 range right there, so there actually is, I think, a correlation between the quantitation and what you are asking for I think is totally valid, and if the microbiology is done right with transport of organisms and they are not dying off, et cetera, things are going to match up pretty well.

Unfortunately, in many situations, the state of microbiology is a sorry one.

DR. LEGGETT: Thank you.

The next speaker will be Dr. Powers, who is going to talk about Clinical Trial Design Considerations for Future Guidance.

Clinical Trial in ABS

Considerations for Future Guidance

DR. POWERS: What I would like to do is to answer Dr. Brown's question here, how we are going to pull together the information that Drs. Gwaltney and Sydnor have showed us this morning about the disease, and then what Drs. Kraus and Pohlman have showed us about our internal review of the medical literature as well as what we have been seeing in these clinical trials, and try to make some proposals for an some things to ask the committee about for what would go into a future guidance in this disease.

[Slide.]

The first issue I would like to address is why do we need to readdress the 1998 guidance, and you can see probably from Dr. Pohlman's presentation what we are getting and why we want to look at this question.

The second one is something that anybody should do in research, whether it is clinical or laboratory research. What is the question we are trying to answer when we look at these trials, and then go into three points about considerations in clinical trial design and acute bacterial sinusitis, that is, defining the disease in the patient population, and you have heard a lot about that this morning, but how can we translate that into a guidance going forward.

The types of studies that one might do and how one measures the endpoints, and even as importantly, how one evaluates those endpoints in patients with acute bacterial disease, and then finally make some proposals for discussion after lunch about going forwards.

[Slide.]

So, how did we get to this point where we wanted to talk about redoing this guidance? Well, discussions at previous advisory committees here in reference, as Dr. Patterson said earlier, otitis media, a workshop last November co-sponsored with the Infectious Disease Society

of America, as well as PhRMA, an international meeting, such as the International Conference on Harmonization.

All of these bodies have discussed selection of non-inferiority margins in clinical trials, is it just statistical or how does it impact clinically? It actually has a very important clinical significance, and that is lack of an adequate selection of a non-inferiority margin means one cannot ensure adequacy of any drug over placebo in that setting.

IN other words, if you took one of our clinical-only trials and had added a third arm to that trial, which included placebo, would either the control or the test drug have been more effective than placebo in that trial design.

[Slide.]

So, the results of all those previous meetings led to an agreement that we would examine previous placebo-controlled trials in each disease to select the appropriate margin, also known as the delta, and we agreed that there was no 10 percent margin for all disease indications, but this entails reviewing all of the pertinent studies in a given disease, not just the studies which show a benefit, so that we can get an overall view of what the studies actually show for this disease.

So, we internally did our review of the placebo-controlled trials in acute bacterial sinusitis, which

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revealed several issues, not only about the potential margin, but some other features about study design that we wanted to address today.

[Slide.]

So, what do we learn from looking at these previous placebo-controlled trials? Well, these trials provide some clues that antimicrobials may be effective in shortening the duration of symptoms in acute bacterial sinusitis.

But relative to the question Dr. Poretz asked, we may all believe--and I think we all think around the table here--that antimicrobials do something for this disease as referable to the question that you asked of Dr. Sydnor earlier.

What these trials don't allow us to do is to come up with an accurate assessment of the magnitude of that benefit in acute bacterial sinusitis. That remains unknown and may be actually small, so we need to discuss other study designs other than non-inferiority trials.

We also want to discuss some other issues with acute bacterial sinus trials, which became apparent as a part of this review. So, this raises a very important question.

[Slide.]

What are we actually trying to measure in clinical trials of acute bacterial sinusitis? One could raise the point that what we really want to know is the, quote, unquote, "true" benefit of antimicrobials as sole therapy in bacterially defined disease without any other symptomatic therapies.

Or one could make the case that what we really want to look at is what is the added benefit of antimicrobials above and beyond the effect of symptomatic non-antimicrobial therapies in patients with bacterially defined disease.

Now, as Dr. Gwaltney just said at the end of the last session here, we don't even know what the benefit of symptomatic therapy is in this disease.

But one might say that the second question is more appropriate because of decongestants, nasal saline, or anti-inflammatory agents are effective in and of themselves, there is no need for antimicrobial agents in this disease, and those other therapies do not result in the problem of antimicrobial resistance.

As we know, acute bacterial sinusitis is the fifth most common reason for prescribing antimicrobials in the ambulatory setting, and therefore, may also be one of the major drivers of antimicrobial resistance, as well.

[Slide.]

Well, one could make the case that antimicrobials would logically have the greatest effect in patients with bacterial disease, and, in fact, the FDA has recently put out a labeling rule, so that each antibacterial drug will have, in their label, information informing clinicians that prescribing antibacterial agents in the absence of bacterial infection is likely to promote the spread of antimicrobial resistance.

These previous placebo-controlled trials seem to confirm that there is lack of efficacy in the populations that are less likely to have bacterial disease, so given this issue of resistance, should we use anti-inflammatory drugs if what we are really looking at is an anti-inflammatory effect of antimicrobials.

Use of antimicrobials in the non-bacterial disease-defined population would really seem to contradict current appropriate use guidelines, and clinical guidelines do recommend waiting 7 days specifically to try to address the issue of selecting the population most likely to have bacterial illness.

[Slide.]

In terms of a clinical trial, though, what is the effect of including patients with non-bacterial disease in a clinical trial? In the setting of a non-inferiority trial, what this actually does is bias the conclusion

towards non-inferiority when, in fact, there may be true differences between drugs, and as I said, one way to look at this is if you added a third arm, which was placebo, into that trial, would either of those drugs have been more effective than placebo.

On the other hand, including patients with viral disease in a placebo-controlled trials biases the conclusion toward no difference from placebo, when there may be important differences between the drugs and placebo.

Including higher proportions of patients with non-bacterial disease results even so with less measured treatment effect of antimicrobials. So, even though you may observe a treatment effect, it is going to be less than what you would have seen if there were only people with bacterial disease in the trial.

This may explain the minimal or no benefit in many of these previous placebo-controlled trials, as the inclusion criteria in many of these did not specify that the patients had to have bacterial disease, nor did they look for bacterial disease by means of sinus punctures.

[Slide.]

As you heard from Dr. Kraus this morning, our conclusions from the review of the literature on correlating clinical signs and symptoms and radiography with sinus puncture, showed that the more rigorous the

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criteria, that seemed to select for a higher proportion of patients who had bacterial disease based on sinus puncture.

However, even the most rigorous criteria would still allow inclusion of maybe between 20 and 40 percent of patients who do not have bacterial disease into these trials.

One of the questions that was asked yesterday was what happens when you include those people in the trial, what is the statistical effect, and I am going to show you that in a minute.

There are no adequately sized prospective, reproduced studies that allow us to adequately select clinical or radiographic criteria which would select patients with bacterial disease. Even when we start looking at combinations of these, we still end up with perhaps, at best, 60 percent of people with bacterial illness.

While 7 days of symptoms is a good way to select patients in clinical practice, I want to raise the question of whether you would want to think about this in a different way when evaluating a clinical trial.

If one uses sinus puncture to define the patients at baseline, it wouldn't matter whether the patient had 7 days of symptoms or not, and I am going to reference this

in a minute to trials, as Dr. Kraus said, with neuraminidase inhibitors.

We know from those drugs that the antimicrobial agent has its effect earliest in the course of the disease. We don't know whether that is the case for acute bacterial sinusitis or not. Is it possible that if we waited 7 days in everybody and then gave them the drugs in the setting of a placebo-controlled trial, that the drugs may have less of an effect because they are on their way to getting better already, and remains unknown.

[Slide.]

Well, as you have heard from Drs. Gwaltney and Sydnor this morning, sinus puncture remains the gold standard. What has been the issue with using it? It is considered unpalatable by many people, but newer procedures may obviate some of this discomfort, and, in fact, are similar in performance to nasal endoscopy in that they are going through the nose instead of what people have described as going up through the gums.

You saw the film this morning that shows that procedure, which is fairly the same as nasal endoscopy except, as the film showed, you go 10 mm further into the sinus instead of leaving the catheter up inside the nose.

We have heard that there is less than optimal accuracy with nasal endoscopy especially for certain

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organisms like Staph aureus where the correlation was actually very poor, not surprising there since we know that the middle meatus is not normally sterile and you can find Staph aureus in the nose normally.

Also, previous studies on nasopharyngeal and throat cultures showed a high level of discordance between the organisms found either in the pharynx or the throat and what was actually found in the sinus, and Dr. Wald's study looked at this in children, and Evans did this in adults, so in neither population was there a good correlation.

[Slide.]

Looking through the Advisory Committee presentations in 1994, 1997, and 1998, about this disease, several questions kept coming up again and again, and I wanted to address some of these here.

Is sinus puncture therapeutic all by itself? Well, it may be therapeutic all by itself. We know that drainage of closed space infections in infectious disease usually is a good thing, however, in the clinical trial, this effect would be evenly distributed across arms of the trial.

We would expect that perhaps the effect of puncture should be small relative to the effect of antimicrobials. We don't know that answer, but if the effect of puncture is so great, one could question whether

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puncture should be the treatment, which used to be the treatment in the pre-antibiotic era, and yet as you have heard this morning, we have never proven that antimicrobials are superior to just doing the puncture, so one could question the benefit of antimicrobials in this setting.

The other issue is don't puncture and antimicrobials do two different things. We know if we want to reference otitis media, that antimicrobials don't make the fluid in the ear go away. We would not expect that antimicrobials would make the fluid in your sinus go away and really what we might be doing with antimicrobials is addressing residual inflammation caused by tissue invasion of the pathogens.

[Slide.]

So, here is another very big concern and that is that sinus punctures are not done in clinical practice, so if they are not done in clinical practice and we do trials based on sinus puncture, how does this replicate how people are going to use the drugs out in the community.

Well, we could sort of put this in the era of been there, done that. Most of the prior placebo-controlled trials that use clinical entry criteria show minimal, if any, benefit for antimicrobials in acute bacterial sinusitis. If one is very concerned about this,

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we could stop now and say you don't use to use antimicrobials. We don't believe that is the case either.

So, perhaps what we need to do is use better definitions out in clinical practice of who actually gets treated. So, we also need to make this distinction between clinical trials and clinical practice.

In a clinical trial, one does blood draws, laboratory testing, any number of things that aren't done in clinical practice. So, because we want to be able to tell doctors how to use the drug appropriately once it gets out into clinical practice, so that gets to a difference between what the FDA does versus what doctors do out in clinical practice.

What we want to do is approve safe and effective drugs for the disease under study. So, if we then approve a drug that we know is effective, then, somebody else can go out and do a trial that says how is this used out in the community, and we have referred to this as an efficacy trial versus a strategy trial.

Other people in the epidemiologic literature have referred to that as an efficacy trial versus an effectiveness trial, with the effectiveness trial being sort of the strategy trial.

So, if one does a strategy trial of how a drug is used out in practice, and it fails to show a difference

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over placebo, like many of the placebo-controlled trials in this disease have, there are two reasons why that trial may fail.

The first is the drug isn't effective in the disease under study, or the second is that many of the patients studied didn't even have the disease you were trying to study.

If you don't know that the drug is effective first, you don't know which one of these is the reason why the study may not have worked. So, what we are saying is we need to rule out number one first.

We need to make sure we are approving that the drugs are actually effective in the disease under study and then translate that literature out into how clinicians can use these drugs in clinical practice.

[Slide.]

So, what is the actual effect? In your handout this is wrong, I was going through this, this morning, I had these flipped. The 65 percent viral is in the wrong place in your handout, but this slide is correct.

So, what happens if you include a number of people in a clinical trial with viral disease, and what does that do to the sample size of the trial?

This is what happens in a placebo-controlled trial comparing drug to placebo if 65 percent of the people

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in the trial have viral disease, and only 35 percent have true bacterial disease?

Let assume, and we have done this based on what we have seen in prior NDAs. The cure rate comes out to be about 80 percent in all these NDAs. Let's assume that the cure rate with viral disease is about 80 percent at day 10, therefore, it is going to be 80 percent with placebo, as well.

On the other hand, let's take the 35 percent of people with bacterial disease and let's assume, just for the sake of argument, there is a 15 percent treatment effect, so there is an 80 percent cure with the drug and a 65 percent cure with placebo.

When you mush all those people into the trial and it comes out the other end, what you would end up with is an 80 percent cure rate with drug and a 75 percent cure rate with placebo.

In a placebo-controlled trial, to show that magnitude of difference, you would need a sample size of 2,900 patients if you used clinical-only criteria in a placebo-controlled trial.

On the flip side, if you defined the bacterial disease at baseline and all the people had bacterial illness, we then are left with the 80 percent cure rate

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with drug, 65 percent with placebo, which requires a sample size of 370 patients.

So, defining the bacterial disease at baseline also has huge implications for the sample size. Now, you could argue that not everybody you tap at baseline is going to have an organism, but even if you have to increase that by 50 percent, you can see that still does not approach what you would have to do in a clinical-only placebo-controlled trial.

[Slide.]

So, let's apply this to what the guidance says now. As you have heard already this morning several times, we suggest two studies, a microbiologically-based non-comparative trial with presumed eradication of the organism based on clinical outcome as the endpoint, and clinical-based non-inferiority trial with clinical inclusion and outcome criteria, which we referred to as clinical-only study.

The guidance does say you can do a superiority trial in this particular setting. No one has chosen to do so.

[Slide.]

So, what are the issues with this previous guidance and what we have learned from looking at these

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placebo-controlled trials and what we have learned about the disease.

Well, the micro studies presume that there is a correlation between microbiological and clinical outcome. As you heard this morning from Dr. Gwaltney, that has never been shown in this disease.

There are examples of other diseases that have less than optimal correlations of microbiologic and clinical outcomes, and perhaps the one most referable to this illness is acute otitis media.

We just published this in Pediatric Infectious Diseases where we took three of the so-called double tap studies in acute otitis media where children received a baseline tympanocentesis and an on-therapy tympanocentesis 24 to 72 hours into their treatment, and have shown that the correlation actually is less than optimal between microbiologic and clinical outcomes.

Sixty-three percent of children who still have an organism in their ear, at that second episode, are clinically cured at that time.

The pre- and post-therapy microbiologic data, however, are very helpful in ascertaining the contribution of drug to treatment effects, so we do want to be able to see this information.

Where it becomes problematic is when one uses microbiologic information as the sole measure of efficacy in these trials, and you have heard enough between yesterday and today about the issue of microbiologic surrogate markers.

The issue with clinical-only studies is again the issue was selecting a non-inferiority margin. They also may include significant proportions of patients with non-bacterial disease based on what we have heard today, and the issue with timing of measurements of outcomes may not be optimal. But let's address this issue of non-inferiority margins.

[Slide.]

We did a Medline search for placebo-controlled trials plus we looked at the references of those trials. We actually came up with 16 placebo-controlled trials, two of which I haven't included on here because one of them actually has uninterpretable results, a score that I can't actually even figure out, and it is a radiologic score, not a clinical one. So, we left that one off. The 16th one is off at the translator getting it translated from Swedish because I am a little rusty on that disease. So, we are going to evaluate 14 of these today.

If you look at some of the meta-analyses performed on acute bacterial sinusitis trials, they look at

things like blinding and randomization, and they come up with a Jedod score, but when we looked through these, it becomes very obvious you cannot do a meta-analyses on these, because the outcome measures are so drastically different across these trials regardless of the fact whether they are blinded or randomized.

Three trials actually have some bacteriologic information. Two have nasal cultures and one does actually a puncture in a subgroup, but as Dr. Gwaltney said, they don't culture what they got out of the sinus puncture, so it is hard to know what that means.

[Slide.]

There is also widely varying methods of assessment of the outcomes. Again, as Dr. Kraus showed with the correlation literature, it is the same here. They evaluate sinuses instead of patients in some of these trials, which makes it very hard to figure out what the outcomes are.

Some use the clinician's assessment so symptomatic cure, they just tell you the patient is better or the patient is not, but they don't tell you how they measured that.

Some use ad hoc scoring systems for symptomatic cure, some use radiological scoring systems. My personal favorite was the osteal patency where you actually measured

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the pressure at the osteal meatus. What that means clinically we don't know, and the best is nasal cytology, and I would like to hear if Dr. Gwaltney can tell us afterwards what that actually means. How changes in that actually translate into clinical outcomes is unclear.

The other thing is timing of assessment of cure varies widely. Most of them have used fixed time points, anywhere from days to weeks after the end of therapy. Two of them did use time to resolution of symptoms in a Kaplan-Meier curve analysis, but even those used different ways in which they did the Kaplan-Meier analysis.

The one trial that is often quoted by Lindbaek because it shows an effect actually only used pain as the only symptom that they did in that time-to-effect analysis. The other one was the Kaiser trial which us a non-validated symptom scale to actually measure time to effect, as well, so there are two that do that.

Several other trials used a sort of modified time analysis where they looked at day zero, day 3, day 5, day 7, at those fixed time points and then tried to draw a curve that way.

[Slide.]

What I am doing here on this slide is actually not scientifically appropriate. You should not put all

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these trials on one graph like this because they really can't be compared from one to the next.

But to look at this, what we see is there are 14 trials all together. These lines in red are the bacteriologically evaluable subsets. This trial actually only used nasal aspirates through a plastic catheter, and this trial actually did the punctures, but didn't actually do the cultures. That is the one we were talking about, the Rantanen trial.

So, as you can see, only two of these trials actually have a lower bound to the confidence interval, which is actually above zero, that actually show a treatment effect. All these others have lower bounds to the confidence interval, which are not above zero, so they do not show a treatment effect.

The vast majority of these have very small treatment effects, and the mean is on the order of about 4 percent for those treatment trials. If we look at these trials and evaluate these in a little more aspect, this is a trial by Gananca. This trial, the symptom outcome measurement was a fixed time point measurement, which just told you whether the patients were very much improved, improved, or not improved, and don't tell you how that measurement was actually made.

One can also call this trial into question because they did nasal cultures where the most common pathogens are Staph aureus, E. coli, Proteus followed by coagulase-negative Staphylococci. So, how one interprets this, which has a treatment effect of 30-some percent is really unclear.

The second trial, which gets quoted often because it actually shows an effect, is the Lindbaek trial, which uses the time to event analysis, but again, that time to event analysis is based only on pain, no other symptoms, so we don't know how the other symptoms actually get better in that particular setting.

[Slide.]

So, as I went through this, the point estimates in the majority of these studies show a small benefit. Of the two trials that actually looked at the subgroups that had bacterial disease, one shows an effect of +25 percent, the other one goes in the opposite direction, -12 percent. So, again, they are going in vastly opposite directions.

The other thing that is very interesting about these studies, they all have very small numbers of patients, which is why those confidence intervals are so wide, as well.

[Slide.]

So, what do we do with that information? We may believe that antimicrobials have an effect on this disease, and the point estimates all lean toward the positive, so that would support that hypothesis. What it doesn't allow us to do is to select an accurate margin.

If you were going to pick it even just based on the point estimates, you would come with a mean average of 4 percent. The guidance, as it was done in the past, suggested what would end up being about a 15 percent margin for these trials, which is clearly not appropriate based on what we know from the placebo-controlled trials and would not allow one to rule out any benefit over placebo in these illnesses.

The ICH-E10 document suggests choosing trial designs other than a non-inferiority margin when the margin is now known, again, because we cannot ensure benefit of any drug over placebo in this setting.

Again, we cannot scientifically justify saying, well, I know antibacterials work in this disease, so I think you should just pick a 10 percent margin. That isn't really scientifically legitimate to do that.

So, are there other types of trial designs we could look at? Well, there is dose-response trial design or what we could call a placebo-controlled trial, which really is more accurately a superiority trial versus other

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symptomatic therapies, and this may be more palatable to patients because you are not just sending them out the door with absolutely nothing. You are at least giving them something that may make them feel better although again we don't know the effect of these symptomatic therapies.

The other issue is that we could design a trial like this to be an early escape trial where, after so many days, if the patient is not improved, they could then be switched over to receive antimicrobial in that placebo arm.

[Slide.]

So, if we did a trial that looked at antimicrobials plus other symptomatic therapies versus other symptomatic therapies alone, there is no issue about selecting a non-inferiority margin since it's a superiority trial. The trial has its own internal validity since there is a direct comparison rather than an indirect comparison with no antimicrobial therapy, and placebo-controlled trials in this disease have been suggested by other independent reviews.

A recent Cochrane review, and I quote it here, says, "Given the small number of trials with heterogeneous results, additional placebo-controlled trials are needed to evaluate the efficacy of antibiotics in this disease."

[Slide.]

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How about the ethical considerations of not giving people antimicrobials in this disease? Well, there are rare side effects, but they are serious that are associated with acute bacterial sinusitis. As Dr. Fleming answered when he was asked this question this morning, one must also balance the risk of adverse outcomes of sinusitis with the risk of adverse outcomes of giving the antimicrobial itself.

We are actually doing an analysis right now of our database to actually look at what are the serious adverse events related to antimicrobials, and Dr. Albrecht pointed this out when we were doing our practice sessions. It seems like with every antimicrobial we see, we notice these bad side effects in the sinusitis group.

That might just be because there are so many patients studied with bacterial sinusitis in NDA databases. Again, there is no data the antimicrobials actually decrease this risk of complications. That doesn't mean they don't. It means that the sample size for such a trial would be very, very large to actually prove that difference.

The complications may be due, however, to altered host anatomy or other factors.

When I looked at all these placebo-controlled trials, there is 1 patient out of those 14 placebo-

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controlled trials who went on to get a brain abscess, and it was with *Streptococcus anginosus*, not with the usual organisms.

[Slide.]

Have we studied other infectious diseases that actually have higher mortality and complication rates in placebo-controlled trials? Yes, we have. Influenza drugs have been studied as placebo-controlled trials despite the availability of older drugs.

The mortality in an influenza outbreak setting ranges anywhere from 10 to 600 per 100,000 depending on whether they are healthy or chronically ill patients, much higher than what we would expect in outcomes with acute bacterial sinusitis.

How do they do this? They select exclusion criteria to minimize the risk.

Are there some ways we might be able to do this? Well, most brain abscesses associated with sinusitis seem to be from the frontal sinuses and cavernous sinus thrombosis may be from sphenoidal disease.

[Slide.]

So, could we exclude people who have frontal and sphenoidal disease? This is one of the questions we want to ask the committee after lunch, as this may be one way to do it.

The other thing is if we are going to do bacteriology on all patients at baseline, could we exclude patients with certain organisms? Microaerophilic streptococci like those in the Strep anginosus group are associated with 70 percent of brain abscesses.

Streptococcus pneumoniae and Hemophilus influenzae occur in less than 1 percent of brain abscesses, so the common organisms associated with this disease are not the common organisms associated with the complications.

The other problem is excluding severe disease, but there is several issues with excluding severe disease.

[Slide.]

The first one is how do we actually define it, and we addressed this yesterday when we were talking about diabetic foot infections. No criteria exists such as that that exists for community-acquired pneumonia if one defines severity as predicting outcomes.

Dr. Anon told me at the break that perhaps there is some validated scale, but in our search we didn't discover that, so if there is one out there, we would really like to see it.

Patients with facial swelling may actually have a different disease. They may have periorbital cellulitis as a complication of sinusitis, and that is not sinusitis by itself.

The exclusion criteria used in previous placebo-controlled trials has been something as minimal as fever. If you exclude people with fever, you may actually be excluding the people that have the bacterial disease, and that may explain why some of these results show such a minimal effect.

So, the patients with what has been called severe disease in previous trials may actually be the ones most likely to benefit from antimicrobials.

[Slide.]

So, what are the implications for drug development? Well, clinical-only trials can be very attractive to drug sponsors because as they are currently designed, they afford a very low risk for failure.

If you put a placebo arm into these trials, it would be unlikely that either the control drug or the test drug would be able to be more effective than placebo. So, proof from placebo-controlled trials that sinusitis does not need treatment in some proportion of patients would be a great public health advance by limiting antimicrobial use to those most likely to benefit, however, from the sponsor's point of view, this would decrease the market share.

As we have heard at these discussions at ICAAC, that antimicrobials are already not very profitable relative to other drug classes.

On the other hand, it would afford the opportunity for smaller trials and more streamlined development programs by using small numbers of trials and actually using supportive data from like community-acquired pneumonia trials and one rigorous sinusitis trial, which gets to what we have been saying about streamlined drug development, less data, but higher quality data.

[Slide.]

Let me show you some examples here of the sample size calculations one could do. We used this example of if you did a non-inferiority trial with a 5 percent margin-- and that is probably not correct because the mean margin, as we saw from the placebo-controlled trials is 4 percent-- you would have to do a 2,700 patient non-inferiority trial to be sure that you were more effective than placebo.

Placebo with a 10-day endpoint would be 780 patients, and placebo using a time-to-resolution endpoint would be 520 patients total in the trial.

If you allow some more aggressive assumptions, such as a 10 percent non-inferiority margin, which is clearly not supported by the placebo-controlled trials, you could do a trial with 670 patients, a placebo-controlled

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trial in that setting would be 370, and placebo with a time-to-resolution endpoint would be only 250 patients.

What are we seeing now? The current sample sizes of acute bacterial sinusitis databases from the 10 NDAs Dr. Pohlman presented have an average of 683 patients per drug in the clinical-only trials, and an average of 584 patients in the micro trials. That is about 1,100 patients per database.

[Slide.]

Let's finally finish up with the appropriateness of timing in this disease. The most appropriate measurement would probably examine resolution of signs and symptoms as Dr. Fleming talked about this morning.

Radiographic scores are not validated and we have heard this morning that they don't correlate with signs and symptoms anyway. The x-ray may resolve long beyond the time of signs and symptoms.

The correlation with microbiological surrogate endpoints and clinical outcomes has not been demonstrated to date. I don't want to steal Dr. Anon's thunder, but hopefully he is going to tell us about some microbiologic information of how to obtain it in this disease, which we are very interested in, but we cannot accept micrologic endpoints as the sole measure of efficacy in acute

bacterial sinusitis without knowing how that correlates or is validated actually with clinical outcomes.

The time to resolution of disease may be most appropriate in self-resolving diseases. Have we used time-to-resolution endpoints in other infections? Yes, we have, the influenza trials and also trials in traveler's diarrhea, which are both self-resolving diseases, for the most part, use exactly this kind of analysis. This is what I wanted to show you.

[Slide.]

This is the time-to-event analysis in a clinical trial based for the approval of oseltamivir, a neuraminidase inhibitor. As you can see, even at 480 hours, almost everybody is better whether they received placebo, which is the solid line, or one of two doses of oseltamivir.

If one were to evaluate the trial out here, and if you did a fixed time point in this influenza trial, this drug would never have been more effective than placebo. Even though this is still a small benefit out here of the drug compared to placebo, the sample size necessary to demonstrate that would have been exceedingly large.

On the other hand, if you moved back here to an earlier time point, you can see the difference between drug and placebo is much greater and therefore you can use a

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small sample size, as well. So, doing an analysis like in acute bacterial sinusitis may be able to allow us to demonstrate a bigger difference between drug and placebo in a smaller sample size.

Again, there is an issue with this and that is how do you measure this. In influenza trials, they measured this using twice daily patient diaries that were actually validated by the drug sponsor.

This is one of the things I want to bring up for academic investigators to help us. What we have noticed is that when we look back through these trials, if the drug sponsor develops this scoring system, they keep it. It is proprietary information, and if you look back through this trial, it says that the sponsor has this on file, and there is a reason why, because if they spent all the money doing this validation program, they don't want their competitors having this validation scale.

So, what we could really benefit from is if somebody out in academics gives us a validated scale that we can all use across these trials.

[Slide.]

So, what are our proposals for going forward? Well, we would like to propose defining the population with bacterial disease at baseline by sinus puncture. We would suggest--and we would like some more discussion about this

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this afternoon--that this not necessarily requires 7 days of symptoms, again because if the benefit of antimicrobials is early in the disease, we may miss that if we wait 7 days into the treatment.

This may actually result in fewer punctures. Our hope that doing the micro-only trials would result in fewer punctures did not pan out. We are tapping almost 600 people per drug right now. Perhaps this would improve the selection criteria for clinical practice, as well, and this is one of the things I think we feel strongly about. Rather than just using these trials to get a drug approved and on the market, can we use these trials to advance the science, analyze who has bacterial versus viral disease, and pick out the clinical signs and symptoms that may actually predict who clinicians need to treat.

The second thing is superiority trial design of symptomatic therapy versus symptomatic therapy plus an antimicrobial, and we need to discuss appropriate exclusion criteria this afternoon.

The other issue is it is very difficult for us to allow resistance claims for a given antimicrobial in acute bacterial sinusitis when one doesn't know the impact of any organism or any drug. You may give a drug and make the organism go away, which may be resistant to the original therapy, so optimizing pharmacodynamic parameters may make

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the bug go away, what we don't know is how does making the bug go away impact on the resolution of clinical symptoms in this disease.

Thirdly, the endpoint of time to resolution of symptoms, again, we would like to suggest something to the previous influenza trial, but this would require a validation of some patient diaries and looking at those endpoints.

Thanks.

DR. LEGGETT: Dr. Wald.

DR. WALD: I don't know if you want to reserve the discussion for this afternoon, but just in terms of the idea of puncturing early, I think again we have to take into consideration there are probably two populations of patients, one who have urgent disease or severe disease, or whatever we might want to call it, and then a second, much larger group which defines itself by the persistence of respiratory symptoms.

In that group in particular, on the third day, those kids, those adults all look alike, they have a cold. At that point they have a cold, they don't have acute bacterial sinusitis. If we were to puncture them then, I think we would not identify a group of patients who are likely to benefit from antimicrobials.

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DR. LEGGETT: Thank you. Let's go to lunch. We
come back at 1:15 for the open public hearing.

[Whereupon, at 12:25 p.m., the proceedings were
recessed, to be resumed at 1:15 p.m.]

- - -

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

[1:25 p.m.]

Open Public Hearing

DR. LEGGETT: We have one speaker, Dr. Jack Anon, who is from the University of Pittsburgh, who would like to speak on behalf of Paul Ambrose and Ron Jones for approximately 10 to 15 minutes maximum.

Is there anyone else in the audience who would like to speak during this open session?

[No response.]

DR. LEGGETT: I would like to read the following for general matters meetings, such as this guidance document review.

Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decisionmaking. To ensure such transparency at the open public hearing session of the Advisory Committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with any company or any group that is likely to be impacted by the topic of this

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Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have any such financial relationships. If you choose not to address the issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

Dr. Anon.

DR. ANON: Thank you.

First of all, I paid for my own ticket and everything for the meeting. I have had consulting work, as I mentioned earlier, with GlaxoSmithKline, Aventis, Bayer, Bristol-Myers, and I think that's about it.

If I left anybody, I apologize, but I have done work for a lot of companies, but basically, research and lecturing, et cetera.

[Slide.]

What I would like to do is present a new technique that we have developed called serial sinus sampling, and if anybody has a really cool name for this, we would appreciate it.

[Slide.]

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Paul Ambrose is here in the audience, as well as Ron Jones, and the three of us are the main investigators for this.

[Slide.]

As we saw a little bit ago, there are different ways to look at the paranasal sinuses and acute bacterial rhinosinusitis. One technique is use clinical diagnosis alone, supplanted with plain film x-rays, or CT, or ultrasound, with observation and resolution of symptoms.

[Slide.]

Here we see again a plain film x-ray with near fluid level in the patient's left maxillary sinus, which is screen right.

The other way to do it is to do an initial sinus puncture, get bacteriology, and we assume that resolution of symptoms implies resolution of bacteria. Finally, we can do follow-up puncture and culture, and as a matter of fact, Jack Gwaltney, as far as I know, is really the only one that has ever done that in the United States a few years ago in a study, one of the cephalosporins.

[Slide.]

So, what we have done is we have taken the indwelling catheter. This is the video that you saw earlier, the SinoJect, and what we realized, I saw this at a meeting a few years ago and I bought one, brought it

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back, and we were using it to irrigate the sinuses, and it did work, and then we started using it to take bacterial cultures during studies. So, we would tap the patient, take the culture, pull it out, and we were done.

Paul Ambrose and Ron Jones, and some others, and I were sitting down talking one day, and we said, you know, rather than take the sucker out, why don't we leave it in and let's see what happens over the ensuing days.

We will sure you that we are now able to get data from that regarding the bacteriologic time curve kills, as well as pharmacokinetic and pharmacodynamic data.

[Slide.]

This is a pilot study that we just presented at ICAAC recently and we have submitted for publication, and we look at a five-day course of gatifloxacin 400 mg. The patients were 18 years and older, and we looked at symptoms for more than 7 days. Again, this is what we were discussing this morning, and we did have radiologic evaluation to show maxillary air fluid levels, and this was sponsored by Bristol-Myers.

[Slide.]

We then put a catheter in on day one. We withdrew a small specimen, and in the ensuing five days, every day we would draw a small specimen for bacteriologic analysis, and on day 4, we did a

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pharmacokinetic/pharmacodynamic day where the patient stayed in the office, had movies, lunch, books, et cetera, we provided all that, and what we did was we would draw blood and we would draw out of this catheter, material, and we then analyzed it for the gatifloxacin concentrations.

[Slide.]

This is the catheter that we initially started to use and to show you that the future governor of California was our first volunteer. There is the specimen being taken. It was quite painful for him, no, but actually this is the catheters we saw this morning in the system, and it is called the SinoJect.

[Slide.]

What we do is we load the catheter onto the end, pull the stopcock as we showed, put it into lateral nasal wall, and push the button. Number one, we don't have to hold the patient's head as was alluded to this morning, and actually, this is very not uncomfortable. As a matter of fact, I will comment, I think having my tooth drilled is more painful than this.

[Slide.]

Then, we put the lavage tube in and just took a very small amount of material out. The key was not to take out much material each time because we did not want to use it for therapeutics, and also, we did put a small amount of

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saline in at the end of each time, but it was just enough to flush the tube out at the end. Again, we did not want to do anything that would like therapeutics.

[Slide.]

This is actually a picture of the catheter in the maxillary sinus on screen left, and on the right is the x-ray we had actually taken of patients, and it shows the catheter.

By the way, in response to a question earlier, I happened to co-author a book on sinus anatomy a few years ago, and what we know is that 65 percent of sinuses will be below the floor of the nose, 20 percent will be even, and about 20 percent will be above the floor of the nose and intermeatus, so when you do these taps, that is something you need to watch for.

[Slide.]

Here, we plotted out our gatifloxacin exposure of plasma versus sinus, and we see the curves here, which actually match very nicely in the group. If we look at our Cmax's and AUCs, we see our sinus aspirate versus plasma, and I won't go into all the pharmacokinetics of that which is not really important.

[Slide.]

This is our pathogen distribution. We can see here the historical distribution as quoted by Jack Gwaltney

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at 10:15 this morning, 1029.03. We see in our pilot study that our evaluable patients and the rest of our bacteriology very closely match what is historically seen, so that is of interest.

[Slide.]

If we focus in on our Strep pneumo patients, what we found was that in each of the study days, we were able to see the Gram stain, as well as cultures, dramatically drop. We found that our mean time to eradication was 50 hours, which is really the first time we have been able to follow the march of bacteriologic change over the course of therapy.

[Slide.]

So, when we ask the question how long do we need to treat, bacteriologically, in our pilot study, we have shown a median is about 50 hours. What we found was that all the bacteria were gone in 72 hours if we took all comers in the study.

[Slide.]

This is just the 4 Strep pneumos. We got rid of the rest of the bacteria and just focused on what we consider to be the main pathogens. So, yes, the numbers are small, but we wanted to just focus it down.

[Slide.]

Now, the question is what is the relationship of symptoms versus bacteriology. So, what we did was we asked the patients all their symptoms, and we monitored the symptoms versus time to resolution of the bacteria, and what we found was the majority of patients, sinus pain resolved.

Dental pain resolved in everybody, sinus tenderness resolved in everybody, purulent nasal drainage in the majority of patients, we still had 2 with persistent, headache in almost every patient, and facial pressure in almost every patient. Nasal congestion decreased in the majority, as well as postnasal drip.

[Slide.]

So, as we discussed this morning, this is really the first time that we can take the actual bacteriologic time curve kill and correlate it with symptoms as we used in our study. Obviously, as you were discussing this morning, we could look at a more complicated and more complex symptom scoring measure, et cetera, and apply it to make all the studies fairly even throughout if one would look at that.

[Slide.]

Cough and sore throat disappeared on everybody.

[Slide.]

As for our future studies, one thing we are looking at now is we are actually going to look at the inflammatory mediators. As we do the study, we are actually going to sample and send off for the evaluation of that, because as we mentioned this morning, there is a lot of up-regulation of the inflammatory disease process and acute bacterial rhinosinusitis.

As an adjunct therapy, and actually I mentioned this to John Powers when I spoke to him recently, is I think that steroids actually do play a big role here. I will tell you clinically, in our practice, all patients who have acute bacterial rhinosinusitis, we do use steroids to treat, and feel in our hands that we do have improvement, but I don't have science behind that, and I am just throwing that out as a clinical observer, not as a scientist.

That's it and I thank you very much.

DR. LEGGETT: Thank you.

Dr. Anon, a question. Can you tell me more about how long you waited before you chose these people, and how long you waited, did you wait to get a bacteria, or how did you initiate therapy?

DR. ANON: What we did was initially, we took all the comers who had symptoms for more than 7 days and had the symptom complex that we equate to acute bacterial

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rhinosinusitis, and at the 7 days, those are patients that are usually getting worse.

Now, as we moved through the study, it is very labor-intensive, needless to say, and what we did was we actually did endoscopic cultures on some patients, and if it came back as positive, then, we would go ahead and put them in the study the following day, so we waited one day.

I think this is the way to enrich the group of patients. We do find that there is about an 80 percent concordance. As a matter of fact, we did endoscopic cultures on all of our patients, and in our small study, we had 100 percent concordance with endoscopic versus tap.

So, I am not saying it's the gold standard, but it was something we were able to do.

DR. LEGGETT: Dr. Cross.

DR. CROSS: Normally, if we have an indwelling catheter with an abdominal infection, we are very leery of putting any stock in the cultures that we get out of the catheter. I was just wondering whether or not you evaluated the issue of possible contamination when you leave the catheter in the nose over four or five days.

DR. ANON: Contamination of what aspect?

DR. CROSS: Of having other organisms. I mean were you looking only at the loss of your isolate on the initial culture, or had you been doing complete cultures at

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each of those time points, in fact, looking for other organisms, as well?

DR. ANON: What I will do is Ron Jones, if I may defer, he did all of our micro work, so I will allow him to comment.

DR. LEGGETT: Tell us about your potential conflicts of interest.

DR. JONES: Currently, well, let's go back about three years. I am funded by approximately 29 different pharmaceutical companies for various aspects of in-vitro test development, as well as evaluations of new drugs as far as laboratory levels and surveillance studies. Do you need the whole list?

DR. LEGGETT: Go ahead.

DR. JONES: Thank you.

What we did in the studies, as you saw from the outline on one of the slides, is there was daily samples taken over the time period. The paired sample in the beginning was at the ostia of the sinus, as well as the puncture, the paired sample, and the pathogen, and in every instance, was found as part of normal flora of the nose, as well, and was found as a single pathogen in the sample that was taken from the sinus.

Over the subsequent 4 days of sampling, no contaminant emerged at all in the 14 drug-bug pairs that we

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did in the 12-patient population of the pilot. So, as far as an evaluation specifically for contamination, all we can talk about is just the 12 patients, and it did not occur at all in that population.

This is the results at each time. Getting back to an issue that was brought up by Barth Reller about the correlation of semiquantitative use, bacteriology in these types of situations and the correlation with counts, I would go and just say what Barth just said is absolutely correct, about the semiquantitative streaking on plates of the specimens, as well as the correlation with the actual Gram stain smears, was essentially at a 100 percent level, so we can use semiquantitative or move on to using more dilutions and quantitation if needed.

DR. LEGGETT: Thank you.

Ciro.

DR. SUMAYA: With obtaining the sinus aspirate via the SinoJect, how many times has this been done, not only in your experience, but in others, the procedure, and has it been included in children, particularly young children, and have there been any adverse side effects?

DR. ANON: Number one, the SinoJect has been used by a number of sites for clinical studies. As a matter of fact, Jack Gwaltney's group uses it, I believe still?

DR. GWALTNEY: No, we have never used it.

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DR. ANON: I apologize. I know there are some other groups that use it, I don't know how many, I couldn't tell you. No one has ever done an indwelling study before, it has never been done like that. In children, anytime you do an inferior meatal antrostomy, you need to make sure that the maxillary sinus has expanded below or is at the level of the floor of the nose.

While I do a lot of pediatric otolaryngology, all of our studies have been in adults, and I have not done children as have Dr. Wald.

DR. LEGGETT: John.

DR. BRADLEY: In looking at the mechanism of repeated sampling from your system, and knowing that the consistency of the fluid in the sinus can be anywhere from thin to extremely thick, having seen Dr. Gwaltney's slides this morning and having some experience with otitis media in kids, once you get your initial tap, in some of these cases, I would imagine that the mucus and pus is so thick that you may have to irrigate.

Once you irrigate, you sort of set up a change in pathophysiology of the sinus disease itself, and when you go in each day subsequently, I am wondering whether you have to add saline to lavage or whether you can just have someone tip their head back, or whether you put a little catheter through this catheter to fish around this sinus,

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but then if you have a tiny little catheter, you may not get the big hunk of thick pus.

Can you tell me mechanically how reliable daily sampling is?

DR. ANON: First of all, we do not lavage the sinus. When we have really thick mucus, we just put in about maybe 1 cc of non-preservative sterile saline. If you consider that the sinus volume is about 30 cc, I don't think that really affects it.

Number two, yes, we actually did the teapot approach. I don't have photos, but I have had patients, we tried to figure out every mechanism that there is to put the head, and, yes, there were times when we just couldn't get anything. The catheter is very small because that is the way it was designed. Actually, we are looking at doing some research, actually, we have done some research on developing a larger catheter that won't clog, and also we have a stopcock, we are looking at trying to put at the end, so there will be no questions about contamination, aeration, or anything else, and we have got actually designs on the drawing board for that.

The other thing I would like to do, the sinus, if you saw in the photos even from the company, the catheter sits fairly high, and we are also conceptualizing a small curve that we can actually go in a little bit more, so we

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get into the depth of the sinus, and then just pull it back out.

DR. LEGGETT: Don.

DR. PORETZ: You said your patients were on steroids. Were all your patients --

DR. ANON: No, sir, not in the study. My patients that I treat in my office, that are non-study patients, I put them all on corticosteroids.

DR. PORETZ: Are those systemic steroids?

DR. ANON: Yes.

DR. PORETZ: Or inhaled steroids?

DR. ANON: No, as does Jack Gwaltney, I believe, that nasal inhaled steroids do not play a role in the disease, and I believe that it's a rhinosinusitis is the proper term, which is inflammation of the upper airway, and that oral prednisone in our hands is what we use to treat the inflammatory component.

DR. PORETZ: And you treat all your acute sinusitis patients with steroids?

DR. ANON: Yes, all my adults.

DR. PORETZ: In conjunction with antimicrobics?

DR. ANON: Yes.

DR. LEGGETT: Thank you.

Charge to the Committee

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DR. COX: I just wanted to start out first by thanking the presenters today for a series of very insightful and excellent presentations on acute bacterial sinusitis. I think today's discussions and the committee's advice that we receive will be very helpful to us as we revisit and further refine the guidance that we provide with regards to clinical studies in acute bacterial sinusitis.

We have three questions today to guide us through our discussions on several key issues in clinical trial design.

[Slide.]

The first question is: How does one ensure that patients in clinical trials of acute bacterial sinusitis have bacterial disease? Please discuss the methods of obtaining microbiologic data including sinus punctures and nasal endoscopy.

Some of the elements that the committee might want to consider in their discussions, based on what we have heard today, might be the role of diagnostic methods, such as sinus puncture for microbiologic evaluation, methods for obtaining these samples, and then also how a more highly characterized patient population might influence the efficiency of the studies that would be performed in acute bacterial sinusitis.

In addition, we also heard information discussed with regards to clinical and radiographic criteria. We also heard discussions about the duration of symptoms that patients might have who might be eligible for study and also that there may be different populations of patients, those with more urgent disease and those with more persistent disease.

I think this also dovetails some with the method for microbiologic sampling and the timing at which any diagnostic procedure to obtain a microbiologic diagnosis might occur.

[Slide.]

The second question. The second question deals with a couple of issues in clinical trial design.

Please discuss the issues of trial design in the study of acute bacterial sinusitis. Please include in your discussion:

The strengths and limitations of placebo-controlled trials and non-inferiority trial. Please discuss how one determines a non-inferiority margin in non-inferiority trials for this indication.

Also, please discuss the strengths and limitations of comparative microbiologic data.

We have heard discussions today on the challenges of determining a non-inferiority margin based upon the

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available data from studies in acute bacterial sinusitis, and we have also heard some discussion on the issue of placebo-controlled studies and some of the safety provisions that might be included within the trial design, such as certain exclusion criteria or provisions for referral off protocol if safety dictates, for example, in the setting of disease progression.

I think it also deserves comment that many of the clinical trials that we review these days are multinational studies. In looking at these data, the factors that we consider include the relevance of the disease in the population under study to that in the U.S. population, the use of adjunctive therapy, the use of the comparators that might be used in these multinational studies.

It goes without saying for trials, both U.S. and/or studies abroad, it is essential to assure that there are adequate provisions to protect patient safety and also that adequate patient informed consent occurs in the study, whether it be in the U.S. or internationally.

As we move on to the second part of the question, the second part of the question intends to address the issue of the micro-only study, which is often a non-comparative study.

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I think really what we are asking the committee to comment on here is the potential value of adding microbiologic data in a comparative trial.

[Slide.]

Moving on to Question 3. Question 3 asks for advice with regards to the endpoints in trials of acute bacterial sinusitis.

Please discuss the issues of measuring outcomes in patients in trials of acute bacterial sinusitis. Please include in your discussion measuring time-to-resolution of symptoms as an endpoint compared to fixed endpoints.

I think this question speaks to the issue of the research question that we are trying to address in acute bacterial sinusitis. We have heard comments today both talking about fixed endpoints and time-to-resolution endpoints.

I guess just one additional comment I will make here is that one of the other potential considerations here is the effect that using one of these types of endpoints might have on the sample size and the efficiency with which studies of acute bacterial sinusitis could be conducted as it may be influenced by the endpoints that are used to determine the primary efficacy outcome.

With that, I will turn it back to Dr. Leggett.

DR. LEGGETT: Thank you.

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I would like to remind everybody that there is not going to be a vote at the end of this session. It is just for our discussion purposes. Also, several members of the committee have planes to catch, so if we could keep our comments pithy, it would be very helpful.

Committee Discussion

DR. LEGGETT: Regarding the first question, how does one ensure that patients in clinical trials of acute bacterial sinusitis have bacterial disease, would anybody like to start? Janet.

DR. ELASHOFF: I certainly don't have any specific notions about this from a medical point of view. I just want us to keep in mind that however we do the trial, we want to be able to tell physicians who use the antibiotic later, who they should be using it on in a way that they will actually be able to use that information, so that in designing the trial, we need to keep that in mind in terms of how we specify who goes in and who has profited.

DR. LEGGETT: Anyone else? Dr. Bradley, can you start us off?

DR. BRADLEY: I was going to wait until Dr. Wald made a few comments.

DR. WALD: All right. I think, one, we talked a lot today about what the gold standard is, and I think if

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we subject the patient who we suspect--and we can talk about why we suspect it in a moment--if we suspect the diagnosis of acute bacterial sinusitis, if we do a sinus aspiration and we recover organisms in high density or a positive Gram stain that we regard as likely etiologies, then, we know we have acute bacterial sinusitis. I think that is the gold standard and the proof of disease.

I think that I would try to select a population that I thought was highly likely to have bacterial disease, and I would do that on the basis of clinical primarily symptoms because patients don't have that.

The physician examination unfortunately of most patients with acute bacterial sinusitis does not distinguish them from patients with acute rhinitis, so you can't look at a patient and know that they have sinusitis, you can only know that they have respiratory symptoms, so I think we rely very heavily on historical items.

I would again say that there are probably two presentations that we may want to at least stratify for, and the classification that Dr. Gwaltney suggested as urgent, or what I have called in the past "severe" disease, and a second presentation of more persistent symptoms.

The more stringently we describe those two categories, I think the higher likelihood of getting a

positive bacterial aspirate or feeling secure that we are dealing with a population that has acute bacterial disease.

In my studies of children, I have used a 10-day rule, 10 days of respiratory symptoms, either nasal discharge or cough, or both, that were not improving, and again with an emphasis on the "not improving" part because there are many patients with respiratory symptoms that are resolving, but are present at 10 days.

So, I think the more tightly we can describe that population, the more likely we will have identified a group of patients that are different from patients who have simple, uncomplicated viral URI.

DR. LEGGETT: Could you or Dr. Gwaltney give us some specifics about which symptoms, how many symptoms? Should we try to make the symptoms be the same for all the drugs, that sort of thing?

DR. GWALTNEY: I am not quite sure what you mean when you say the symptoms be the same for all the drugs.

DR. LEGGETT: When we looked at the published trials, one trial had just facial pain and the fever, and the other trial had postnasal drip or cough or purulent discharge, what should be the bottom line number of things that need to be there for us to clinically think that this person was more likely to have acute bacterial sinusitis.

DR. GWALTNEY: One of the good things, if a placebo-controlled trial were to be done in which sinus aspirate cultures were taken before onset of treatment, and either a post-therapy culture or the method we saw described by Dr. Anon, if that kind of trial was done, one of the great benefits would be that we, for the first time ever, would have a correlation between symptoms and symptom patterns, and the presence of infection.

So, we would learn a lot, which then would help us in the future maybe, or maybe not, maybe it wouldn't. I would think the thing to do about the symptoms, we have done a number of studies on the common cold, and there are about seven symptoms - sneezing, runny nose, nasal obstruction, cough, sore throat, headache, et cetera, and there are systems that have been designed and pretty well validated based on severity of the symptoms.

The type of data are, of course--what is the word I want--they are non-parametric data, but they still I think are important because the illness is what bothers the patient. So, this system collects these symptoms on a daily basis and the patient quantifies the severity of the data, and this kept up during the course of the illness.

So, not only can you determine the length of the illness, but you can also determine the severity of the individual symptoms, and it would seem to me that that

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would be the kind of a symptom record that would be good to keep in this type of study.

Now, as to what you would require to put the patients in the study, I think Dr. Wald has done a nice job in terms of what she just said. I believe it probably would be of value to enroll patients after a certain duration of illness, because I think the chances of getting a positive bacterial culture would go up if you waited for a week or--a week, to me, would sound like a reasonable period of time--and not being improved. I think we have to keep emphasizing that because it kind of gets lost in the discussion, but it is not just the symptoms are there, they are not improved.

I think with that kind of collection of clinical data and correlating it with results of Gram stain and culture, we could learn a tremendous amount about the clinical picture of the disease in addition to learning whether antibiotics had any benefit in the treatment of the disease.

DR. LEGGETT: What about the use of x-rays and-- did you have something to say, Don?

DR. PORETZ: I just wanted to ask, do you really believe that patients would volunteer to be in a study if there was placebo-controlled arm especially if they go through a sinus puncture?

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You have done this for several years, patients would be willing to be on a placebo arm?

DR. GWALTNEY: I think in the current environment in which I think the public is pretty much aware of the fact that antibiotics are not what you should get all the time when you have an illness, and in talking with physicians, I think there are patients that come in and when they really need antibiotics, will turn them down if, say, they have a strep throat or something, so I don't think there would be any trouble enrolling enough patients to do that, particularly if they were told they were being followed carefully.

I guess there is an advantage of having an indwelling catheter in that you really have a handle on what is going on. You could do a Gram stain every day, do a culture every day, although I am not sure it is necessary to do it daily, so, in addition to monitoring the severity of the patient's illness and determining what is happening, whether they are getting worse or getting better, you have bacteriologic data to guide your treatment, and if somebody seems to be getting in trouble, you can always take them out of the study and treat them.

It would seem to be it would be a pretty safe kind of a study that would be ethically justified on the basis of safety.

I think you could argue do we have enough information now. Medicine is an art obviously and I think there is a fair amount of compelling data that convinces me that antibiotics do work.

I would be honest in doing a trial--although I am not going to be the one to do it--but I do think they work based on what has been published, but I still think it might be worth going on and doing the placebo-controlled trial and settle this issue which has been banging around now for three decades and doesn't seem to be getting resolved.

DR. LEGGETT: Dr. Powers.

DR. POWERS: I think this issue of patients and antibiotics has two sides to it that never gets brought out. One of the placebo-controlled trials that I presented, that was done in Europe, there were approximately 200 or so patients who refused to be in the trial.

A hundred or so refused because they absolutely wanted antibiotics, 72 refused because they absolutely did not want antibiotics, and I think that is the side of the story that we keep forgetting. There are patients who are very willing not to get an antimicrobial in this disease.

DR. LEGGETT: Any other comments?

DR. GWALTNEY: I think it goes without saying the patients who were not treated would be offered treatment at

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the end of the study if they wanted it, so it would not be that they would never receive treatment.

DR. WALD: I think that is important, in fact, the fail-safe might be a whole lot less than 10 days. This is why I think somehow a score is going to be important because I think you would need to have some semi-objective ways to say that a patient was getting worse, or if they were even not improved at 72 hours, you could call that a failure. I mean expect antibiotics to kick in by 72 hours, so if someone was no better according to some score or some schema, then, you could say that they popped out of the study and that they deserved antibiotic therapy. Certainly, if they worsened, that would be a call to drop them out.

So, I think you would need that kind of very close attention to detail, so that patients would be assured that they are not going to be left out there dangling.

Just to go back to I think the question that you asked, which was what are some minimum specific criteria that we are going to use to define the patient groups. I don't know if people felt satisfied.

If we talk about the urgent group, would we want patients to all have fever, do we want them all to have facial pain, do we want them all to have purulent

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discharge, I mean are there some minimal criteria that make physicians want to treat patients urgently, and if there are, what are they.

The second presentation, I think is easy. I really think you really can use duration, and you can use very simple things, because you can't probably ask someone who has got intense headache and a fever to wait 7 days, clearly, you are not going to do that.

So, the patients that you can ask to wait 7 or 8 or 9 days are those patients who have no fever, but have instead these persistent respiratory symptoms which are spoiling their quality of life. It is not killing them, it is just making them uncomfortable.

So, those are the patients I think that we could simply look at duration of simple things like nasal discharge, or cough, or both.

DR. LEGGETT: Would fever, purulent discharge, and facial pain be enough to adequately filter out viral rhinosinusitis in an urgent situation?

DR. WALD: I think you are going to get some influenza in there, there is no question about it. I think it is a much harder group to figure out really who has bacterial disease, and it actually I think heightens the importance of the aspirate.

I mean at 10 days, when someone is still symptomatic and not improving, I feel pretty confident that they have a bacterial component to their disease. At 3 days, you know, you can be pretty miserable with a lot of viral upper respiratory infections, so I think it is harder to sort out, but I think that would be a good beginning, fever, purulent nasal discharge, probably with headache in the older patients maybe with facial pain.

DR. LEGGETT: Would you lump them all in the same group, or would you make sure they are somehow stratified into two separate analyses?

DR. WALD: I think you absolutely have to stratify them.

DR. LEGGETT: What is your opinion about the relative frequency, would we get an "n" big enough to make any sense with that urgent group?

DR. WALD: I have to defer to the adult, the people who care for adults.

DR. GWALTNEY: Maybe Dr. Sydnor can answer this better than I can. It is my impression that the number of people that present in the urgent category is relatively small. I think if you were only to do a study of that group, it would take quite a bit of work and quite a number of sites to do that.

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I really don't know the proportion, but I would say it is probably 1 to 10, or even 1 to more than 10, the ratio between those two groups.

DR. SYDNOR: I would agree with you heartily.

DR. LEGGETT: So, it sounds a lot more feasible in trial design, even though we would like to capture that urgent group, that we sort of limit it to 7 or 10 days of symptoms, and then just allow people to treat the early ones, and not put them in the study.

John.

DR. BRADLEY: I think again that the microbiology is going to be an essential part of the studies and however you design the entry criteria, the stricter you make it, with the more symptoms including fever and pain, duration of disease, that you will enrich for the bacterial components.

But if you ease up on the entry criteria, you will still get some bacterial patients, but they will be fewer as they go into your study, but as you evaluate the two arms of the study, whether it is placebo controlled or comparator controlled, you will be able to track symptom response in both groups.

In terms of the microbiology, which we were discussing this morning, I think either this catheter, which looks like it would work for adults, I have some

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DR. LEGGETT: Dr. Powers, you talked about the correlation between success or the lack of optimal or suboptimal, however, you said, between the cultures in the otitis.

How about the flip side, how about the correlation between failures and persistent bacteria?

DR. POWERS: There is no data to do this obviously in acute bacterial sinusitis. Looking through the NDAs, we had one--

DR. LEGGETT: No, I mean in terms of the otitis.

DR. POWERS: Right, I am just sort of taking that reference. When we looked at this in otitis, it is, and the correlation between clinical failures and people that had a persistent positive culture was very good.

This is something I think back on that we probably should have mentioned back last July when we were going through that otitis media discussion. When we are talking about validating an endpoint, it has got to work in both ways.

It has got to be that microbiological failure predicts clinical failure, but also it has got to go the other way, too, that clinical success has got to be micro success, as well, and what we saw was that is where it fell down, that people who were clinical successes, at least in

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these otitis media studies, 63 percent of those children still had their organism present.

So, that correlation means it has got to go in both ways.

DR. LEGGETT: Don't you think that was a matter of where you chose to draw the line as we saw from the 5-day data, for instance?

DR. POWERS: I think it is. I think that what we are seeing is that it is on-therapy evaluations that become problematic and, sort of referable to our early yesterday discussion during the closed session, when one takes a microbiologic specimen at the time that the antimicrobial is on-board, you also don't really know what that means at that time.

As Dr. Bradley is saying, perhaps what we would need to do is also do the clinical and microbiologic evaluations at the same time, so that we can correlate those two together, and also perhaps do it later on when the antimicrobial is not on-board.

As far as the double tap studies in otitis, that is not the way they are done. It is done earlier in the disease when the drug is still around.

DR. LEGGETT: Ciro.

DR. SUMAYA: Although I realize that the urgent, acutely severe form, in contrast to the long-term

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persistent 7 to 10 days of non-improvement in a number of signs and symptoms, the severe form or urgent form, I would hate to just displace it, realizing that the numbers may be small, because I think it may provide some nice information clinical to microbiologic associations of correlates as opposed to the more persistent group, and it is one where I think we can obviously learn significantly about the microbial status in that type of patient.

I think it will pay off although the numbers I have to admit would be small, and perhaps this could be a second stage study after we do one that is more with the persistent group.

DR. LEGGETT: Jan.

DR. PATTERSON: As far as the criteria, I agree with what has already been said. I think it would be useful to the clinical symptoms to differentiate between urgent and elective, and, like Ciro, I think we probably shouldn't exclude those urgent just because they are small numbers, because even if they may be less numbers, we may be more likely to see an effect of antibiotics with those.

I want to clarify I am not against international studies and I think they are actually very helpful especially in terms of generalizability and in enrolling large numbers of patients and finding patients that haven't been pre-treated.

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I think actually for this particular infection, that there are U.S. IRBs these days even that would accept a placebo-controlled trial and actually have accepted that.

I mean I think that a placebo-controlled trial for elective, people that fit in an elective category, not the urgent category, would not be an unreasonable thing, but I was just concerned about the appearance of saying that if all of our U.S. IRBs think it is unethical, then, why should we ask other countries to do that, so I was just concerned about the appearance of that.

Anyway, we have kind of touched on some other things. I think that the idea of a study with a puncture versus antibiotics, or a puncture versus antibiotics plus puncture is actually very interesting, because if indeed the puncture is quite helpful in relieving the symptoms and maybe ultimately the disease, that would be I think very helpful to know.

Another point that John made earlier, that we also discussed previously at these meetings, is the idea of streamlined drug development, and if a drug has studies that show it is effective for community-acquired pneumonia, that it might strengthen the case for other bacterial respiratory infections like this, but that we do need to have some specific studies looking at sinusitis because

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there are some other organisms, like staph and strep, that aren't involved in community-acquired pneumonia.

DR. LEGGETT: Would several of you care to address the radiologic thing? Will the use of radiologic criteria likely enhance the bacterial yield?

DR. WALD: I think imaging gives you very general information, and as the study that Dr. Gwaltney presented, abnormalities on images are the rule rather than the exception in anybody who has upper respiratory symptoms.

So, the way I think that they are useful is twofold. One, there aren't too many otolaryngologists who would do even a sinus aspiration without a road map, because just as Jack Anon was saying before, you want to know if the floor of the nose is above or below the floor of the sinus, so most people are not going to want to engage in even a relatively simple invasive procedure without know what the anatomy and the landmarks are.

Secondly, I think if you happened on the extraordinary patient who had a normal image, of course, you would exclude them from the study. So, I think normal images tell you the patient doesn't have sinusitis, abnormal images don't tell you that the patient does have acute bacterial sinusitis. They tell you that the patient has sinus inflammation, but for our purposes, especially if

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we are thinking about aspiration, I think some image is necessary.

DR. LEGGETT: Would a regular x-ray be enough, looking at the things that Dr. Gwaltney or whoever pointed out with the air fluid levels?

DR. WALD: It would be for me. I still like plain radiographs. I think that CTs are certainly a much more sensitive test. They tell you a lot more because you are looking at really many images of the paranasal sinuses, not just one cumulative image, but I think for this purpose, a plain x-ray would suffice.

DR. LEGGETT: The issue of nasal endoscopy for culturing, anyone's feelings? The little data that I saw didn't make me very excited despite the fact that in the small pilot trial of Dr. Anon, it seemed to correlate, but we have other trials that didn't.

Is anyone in gross disagreement? Barth, what about your take on nasal endoscopy cultures?

DR. RELLER: I don't think you can make a diagnosis of bacterial sinusitis without a culture, and I think the cultures are of value in relation to the quality of the specimen. I think only the aspirates can be unequivocally interpreted at this point.

DR. LEGGETT: What are people's takes on a trial design, such as was shown with Dr. Anon, where we do the

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sinus tap, wait a day to see if we have bacteria, and then begin treatment in this group, not the urgent group, but in the group that's 7 days? Janet.

DR. ELASHOFF: While everybody else is thinking, it means an extra, a definitely two-visit start-up to the trial, so logistically, it is more complicated and it is more expensive. I think you would have to know that you really wanted to do it that way.

I guess you could always have a rule that they are not counted in the trial if they didn't have it, or they are analyzed separately or whatever.

DR. LEGGETT: Dr. Gwaltney.

DR. GWALTNEY: We also have the advantage of the Gram stain, and there is a pretty good correlation, so if the Gram stain was positive, of course, you have got to have, as someone said, 10^5 organisms roughly to have a positive Gram stain, but if that were positive, I think that would be good enough evidence to go on.

The limited amount of information we had from Dr. Anon, which is wonderful information, in that case, with the Pneumococcus, there was a perfect correlation in those four cases.

DR. LEGGETT: But we may not be with Hemophilus or Moraxella.

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DR. GWALTNEY: Well, I showed you the Gram stain with the H. flu, and I think there is no reason to think you probably wouldn't see the same with those other organisms.

DR. LEGGETT: Jan.

DR. PATTERSON: Another thing that came up in the otitis media discussion was the effect of the pneumococcal conjugate vaccine, since with otitis, that is where we see the really severe distinct disease, and if it is being used more widely, how will that affect this disease? I mean will it change the character of this disease, will we see even less urgent or severe than we used to.

DR. LEGGETT: Ellen.

DR. WALD: I think on balance, the impact of the pneumococcal conjugate vaccine on otitis has been very small. People calculate overall cases, it is about 6 percent. For the type-specific pneumococcus, it is higher than that, but we are seeing replacement serotypes already, so I wouldn't count on it making a very big difference in the epidemiology especially in adults, although certainly some adults may harbor the same organisms as their kids.

DR. LEGGETT: John.

DR. BRADLEY: In looking at the original lecture earlier today by Renata Albrecht saying that in the draft guidance from 1999, they were looking for 25 pneumococcal

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isolates, and we have got 4 right here, the potential to use techniques like this, to use pretty stringent enrollment criteria to enrich for bacterial isolates, has the potential to incredibly fast-track the data analysis and potential approval of a drug.

I mean 4 out of 25, as a pediatrician, I don't know if gatifloxacin has an approval for sinusitis in adults, but if they didn't, they would be well on their way.

In terms of the numbers that Dr. Powers presented earlier, looking at possible drug effect with the numbers, and knowing that there is probably a whole set of pharmaceutical companies waiting to tap into Dr. Anon's system, John or Ed, how many patients do you think would be required, or Dr. Albrecht, if the microbiology were there and you had a system with clinical, as well as microbiologic endpoints?

DR. POWERS: I think that is the data I actually showed. Remember, the reason why we were using only 25 organisms was because we had a separate microbiological trial and a separate clinical trial, so we weren't linking the two together.

We were making an assumption there that if the drug came out non-inferior in the clinical-only trial, we just wanted to see that there was microbiologic efficacy in

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the micro trial. Well, what we presented today is those two things don't link together.

What we would like to see is obviously a higher number because we would hope that if you use sinus aspirates to get people into the study, everybody is going to have a positive culture. That number 25 wouldn't even be an issue anymore because we would hope that there would be plenty of people.

What I showed is that using a time-to-resolution endpoint, that would be about 250 people in the trial, so this way we would get more microbiological data and have stronger conclusions at the end of the day.

DR. COX: The hope is here that with the more highly characterized patient population, I mean you have seen the numbers that we have been seeing. The question is, is could it be done more efficiently with a more highly characterized population. What that exact number would be is still another issue that would be determined by statistical considerations, et cetera, but I think a more highly characterized population might reduce the number some.

DR. LEGGETT: A point was made about the potential placebo-controlled trial of probably trying to enrich it, of missing out on the thinking we saw in urgent,

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but it was actually an emergent, frontal sinus, something like that.

Those still represent cases of sinusitis. Should a trial for a new drug be limited to maxillary sinusitis given the fact that it's the most common form, or what do we do about those exclusions that were suggested of micro aerophilic strep in the frontal sinusitis? Alan.

DR. CROSS: It seems that we really wouldn't have a sufficient number of cases of the frontal and sphenoid to actually decide whether or not they behave differently than the maxillary. So, it seems that you would have to probably substratify for that upfront and then the issue is will we actually be able to get any microbiologic data.

I think from what we have heard, the real importance is to hook up the microbiologic data with the therapy, and I think that by including those other sinuses, it would fall outside the goals of the study.

DR. LEGGETT: Ellen

DR. WALD: I agree with that, and it has sort of been a sad observation on my part that at least 50 percent of the patients who present with complications, present with complications that is their presenting illness. It isn't as if they had a prodrome that we could have identified rightly and treated them and prevented it. They

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come in with that complication whether it is an orbital abscess or a brain abscess.

So, although I like to think that we treat sinusitis and prevent complications, I think that isn't something we can look at in this context.

DR. LEGGETT: Joan.

DR. HILTON: For me, the clinical endpoint still isn't very well defined. I wonder if we are looking for a resolution of symptoms, and if that comes from patient diaries.

DR. LEGGETT: Can we address that as we get to the clinical endpoints?

DR. HILTON: Okay.

DR. LEGGETT: I am just trying to beat this Question No. 1 to death.

DR. HILTON: Sure.

DR. LEGGETT: In that regard, Ed, when you talk to us, is there something that I didn't jot down to have us address?

DR. COX: I think we are all set with Question 1, if you want to move on. Thanks.

DR. LEGGETT: Tom.

DR. FLEMING: Before we leave it, there are a couple of issues that I wanted to pursue, but I wanted to make sure because I have been very interested in my

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clinical colleagues' insights here as to how we would ideally define the eligibility for this population.

The motivation is clear that we want to enrich this population for those with bacterial infections, and yet we want to have a population that is representative as best possible of what we could apply in the real world.

Having heard all of this discussion, I am trying to summarize in my own mind where we have come. I have heard from Dr. Wald that we might be looking at a combination of urgent cases, as well as for those that aren't, those that would have persistent symptoms for at least 7 days without improvement was clarified, so that we are more likely to be looking at a bacterial population.

Is that essentially where we are from the consensus of what I am hearing, which would mean that sinus punctures wouldn't be considered to be an integral part of defining the eligibility criteria, or am I missing--is somebody willing to summarize the essence of what we would, by consensus, define to be the patient capture population?

DR. LEGGETT: My understanding may be flawed, but it was my understanding that everyone was going to get a sinus puncture and then we would follow them with clinical endpoints, so that we could link the microbiology with the clinical endpoint.

DR. FLEMING: So, basically, it would be defining the population as I had summarized from Dr. Wald, but all of them would have had a sinus puncture to have truly done the best we could to maximize the percentage that had bacterial infection.

DR. LEGGETT: Right, so that if you are beyond 7 days, you get that symptom list, and the only way you are going to get into this study is if you have got a fever and signs of severe illness if you are less than 7 days.

DR. LEGGETT: Dr. Gwaltney.

DR. GWALTNEY: The other thing to remember is that although these people may be getting sinusitis, they still have a cold, so they have got the cold illness and then on top of that, the sinusitis illness, and I think that is important to consider in answering your question.

There are two methods that have been used for common cold diagnosis. One is the method of George Jackson, which is based on the quantification of the symptoms, and a minimum symptom score of 6, and that has been used for quite a long time.

Another system is just the idea that a person has to have one or more respiratory symptom on a single day or one respiratory symptom for two or more days, a very liberal criteria, but that has worked pretty good, too.

So, I think that without getting to the specifics, you would want a group of people who meet some kind of criteria like that and have gone the duration of illness, and then you do the aspiration, and then those would be the ones that get enrolled in the clinical trial.

DR. LEGGETT: Go ahead, Tom.

DR. FLEMING: Maybe just a comment and then a question. The comment is I think there is here a lot that I see very attractive because it makes a lot of sense to do the best we can to try to define a population that is maximally bacterial rather than viral.

I think, getting back to Dr. Bradley's question, if we made the assumptions in Dr. Powers' presentation, for example, that if we had entirely a bacterial population, we could increase the cure rate from 65 to 80 percent at 15 percent delta, we could then do that with a trial of about 350 patients, something to keep in mind is as you then have the fraction of people that would, in fact, be bacterial, you then 4-fold increase the sample size.

So, if that was the case for 100 percent bacterial population, if our eligibility were yielding only 50 percent, then, in the spirit of what Dr. Powers' calculation showed, the same size would go up 4-fold. It would take us, then, about 1,200 people to be able to see

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an antimicrobial effect in a population that would only have 50 percent bacterial.

So, the motivation for capturing a population that is much more targeted toward bacterial is really strong. The only uncertainty that I have comes back to a point that I think is related to Dr. Elashoff's very first comment, and that is it is very important for clinical trials to be able to establish efficacy as Dr. Powers' presentation had indicated.

My sense, though, is I always want research to be as applicable and as generalizable as possible to a definable real world population, so once we finish the trial, if we establish that we have efficacy, have we established it in a definable real world population, that we can then go out and be able to apply.

So, if sinus puncture is part of this, my question is would this then be an achievable definable population. Surely, it is well defined, but would the performance of a sinus puncture be something that could be presumed to be fairly widely then implemented after the trial?

DR. LEGGETT: I don't think so, but I think the inference is that particular subgroup, a physician could be educated that they would not offer antibiotics to people that were not in that subgroup, and, in fact, there is an

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ongoing CDC and Emerging Infection Network program called Judicious Use of Antibiotics in Upper Respiratory Symptoms plastering doctors' offices, nursing homes, daycare centers, et cetera, of which many states also have a copy, including Oregon, that we post everywhere, no antibiotics unless... and that list.

DR. FLEMING: Would that "unless" basically be if you weren't in the eligibility criteria, so would that "unless" basically mean if you didn't do a sinus puncture, then, it wouldn't be advised that you proceed?

DR. LEGGETT: No, it would be that you have those symptoms, but you don't have a sinus puncture, so, in other words, you mimic that group, but you don't need a sinus puncture.

DR. FLEMING: What I am not sure about, though, is with the sinus puncture, our intention, of course, is to achieve a much more targeted population with bacterial infection. If we use just the symptoms alone, what we could conceivably have is in the group with the symptoms, but where the physician and patient never went through the sinus puncture, we may have a much lower overall rate of bacterial infection, because we are not filtering out those people who, if they had gotten the sinus puncture, wouldn't have been found to have had a bacterial infection?

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DR. LEGGETT: My thought is we do not exclude those people after the sinus puncture if they don't have bacteria, they are in that group.

DR. FLEMING: Are they still in the trial?

DR. LEGGETT: They are still in the trial.

DR. FLEMING: Then, I am perfectly comfortable, and essentially in the trial, I assume you would be doing some assessments within the subgroup that had the sinus puncture and those that did not.

I am not sure whether you would plan to power the trial accordingly.

DR. LEGGETT: If they had bacteria.

DR. FLEMING: Well, both, because I am interested in both.

DR. WALD: Well, everybody will have had a puncture. That is going to be an entry criteria, it sounds like.

DR. FLEMING: That's true. So, it is going to have to be whether they had bacteria.

DR. WALD: I guess the hope would be that, you know, we are going to collect a lot of information, and that maybe we could then be more predictive after we look at which symptoms and signs are correlated with positive bacteriology, and therefore do a better job even when we

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are not doing sinus punctures in the future, you know, after the study is completed.

DR. FLEMING: So, basically, in this study, as now I am more clearly understanding the way you are proposing this, the sinus puncture will be done routinely, but the results of that will not be used to determine whether someone is eligible.

So, is the sinus puncture doesn't show bacterial infection, that person is still on the trial. That is what you are proposing, so that essentially then it does provide us the ability to have something that is very generalizable. The only limitation from the design that you are saying is if it turns out the sinus puncture shows half the people, in fact, have viral infection, then, we are in the circumstance of needing to do a 1,200 person study rather than a 350 person study.

DR. LEGGETT: John

DR. POWERS: Let me ask a more specific question about something Dr. Gwaltney said, because that is the way I was thinking about it, but then Dr. Gwaltney brought up perhaps an intermediate way to do this, and that is if you are going to do the sinus puncture on everybody at baseline, could you then use the Gram stain as a screening test. If you have a negative Gram stain, they are not

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enrolled in the trial, if they are positive, they go into the trial.

Then, you have got another even more narrowed-down subset. If the person has a positive Gram stain, but still is culture-negative, they could stay in the trial, but we would analyze them separately versus people that Gram stain positive, culture positive.

DR. LEGGETT: Right, so my thought about that was that they go in the trial in the sense that we follow their symptoms and signs throughout, but they don't get drug. If they do have bugs, they get drug.

Could you then compare--

DR. POWERS: We would randomize them. The important point is at what point do they get randomized, that is the important point.

I think what you could do is if somebody comes in, they have signs and symptoms--I mean what I have got written down here is so you have a person that comes in and they have to have a specific duration of illness, a constellation of signs and symptoms, and a positive radiograph, with the radiograph again not being specific, but as Dr. Wald pointed out, probably most people aren't going to stick anything in somebody's sinus until they actually even have that anyway.

When you have those three things, then, you tap the person. You can do a Gram stain right then and there. If your Gram stain is negative, you are out, you are not enrolled in the trial at all. If your Gram stain is positive, you get randomized to placebo or to drug, and then if you are positive culture or not, hopefully, that will even out in both arms.

DR. LEGGETT: Then, we are back to his question of they may not be comparable populations.

DR. FLEMING: But let me see if I follow. So, it's a positive Gram stain, a positive radiograph, and symptoms. That would define your eligible population for the trial. So, the sinus puncture, if it were done or not isn't integral to defining the population.

DR. POWERS: You won't have that positive Gram stain until after you have done the puncture.

DR. FLEMING: So, we are using it.

DR. LEGGETT: Barth, then John.

DR. RELLER: I am wondering if we are not letting perfection getting in the way of good here. To me, it would be totally applicable to clinical practice, and yet achieve the rigor that we have not had heretofore to define those patients as best as we can from what we know, duration, everything that has been said, that have a high

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probability, and the odds favor, done well, that it would be in the order of 60, 70, 80 percent positive cultures.

Then, after this were done, just so that no one would be enrolled unless they had--because that is the only way you can tell whether they really have bacterial disease or not, and this is operating on the premise that the only hope for an antimicrobial effect is in patients with bacterial sinusitis. I mean that is what all the placards and CDC and everybody else has seen, these drugs aren't for people with viral illness, which is the commonplace.

Then, you would for education and clinical practice, I mean nobody is going to ever expect, based on any clinical criteria, that you are going to be able to assess 100 percent accuracy who has bacterial sinusitis. If you could, we wouldn't be here.

Consequently, if you can get 75, 80 percent and say, okay, in audits, Quality Assurance, all of that stuff, you are only treating those people who meet the entry criteria for this trial. They happen to be, in order to be evaluable by FDA, have to have a sinus puncture.

Then, you would be miles ahead of where we are, and it should be that if there are enough patients in that non-bacterial, that you might even be lucky with a placebo in there to show that if they didn't have bacteria, it didn't make any difference relative to placebo.

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Maybe as a segue into Question 2, I was sort of deciding whether to say this with Question 1 or Question 2, but if the pitfalls that we have all been trying to avoid, in the marvelous presentations earlier, I mean this issue of should we have clinical trials or micro-only trials, you know, the clinical, we have thousands of patients enrolled, and at the end of the day, everything that we have seen, we are not even very confident particularly with this--I was very impressed with Dr. Fleming's presentation yesterday and today--we are not even sure that it's better than placebo, and I have grave questions whether we will ever find out with the clinical-only trial.

On the other hand, we also have good information that however important microbiology is, to establish an etiologic diagnosis and to objectively say that there is bacterial infection, it is not a surrogate for what the patients want and what physicians want for their patients, I mean that they get better, and we help them get better if they have got something that we have got a good possibility of helping them with antibiotics if they have the bacterial infection.

So, why not skip all this clinical-only or microbiology and only having one kind of trial, and that is just what we have been talking about, and then the placebo issue, the creep and non-inferiority business.

If you did drug A versus placebo, could you avoid the Pollyanna, the creep, the possibility of lowering standards over time is to say that you are only going to accept all the things that we said, only taps, and that you would not be able to have drug A versus the comparator, or A versus B, unless you had documented objective good evidence of the kind of quality that we are talking about from my previous study with placebo.

Now, I think from what I have heard, that would automatically mean going forward, that you would have a placebo arm, so that then you could have A versus B and a placebo in there. It would increase the numbers a little, but on the other hand, if you had two effective treatments, you would have 2 to 1, treatment versus placebo, and given the numbers of the people who don't want an antibiotic with education, who do, you would be balancing the numbers off that I think people would go for, and then with the microbiology and the numbers that we had earlier, it wouldn't take a lot of patients and then we would have what we really want, that would satisfy all of these things that have been discussed at length.

So, what I would do if I were king, is that there would be tap only, A versus placebo or A versus B with a placebo arm, and the only ones that would be evaluable would be those who had bacterial disease, and then we would

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really know exactly where we stood, and then the future trials could be based on what we got out of something like that.

DR. LEGGETT: John.

DR. BRADLEY: Well put. I think we were all moving towards one clinical trial rather than two separate especially since we have all agreed on the need for better micro.

In doing clinical trials, the way that I envision this is that it is going to be double blind, so that neither the patient nor the doctor will know, and when you have the symptoms that we have laid out as inclusion criteria to get into the trial, I think that you are really getting a highly enriched population for sinus disease that you want to treat.

If you make this a multicenter study, then, the quality of Gram stains, especially given how heterogeneous this fluid is that you get out, I think it is going to make it fairly difficult to use that as an enrollment criteria, as a practical enrollment criteria.

So, to me, a patient comes in, they have got all the symptoms, they meet the criteria, they get their puncture, they get randomized, and neither the doctor nor the patient knows what they are getting, and whether it's placebo versus the experimental drug, which would probably

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be better, or a comparator, to me, that is less relevant than this prospective, double blind assessment.

The other thing is if the Gram stain will be positive if you have got 10^5 or more, there may be people with 10^3 or 10^4 organisms which represent sinus disease that needs to be treated out there that we are going to be missing and excluding from the trial if we exclude people by Gram stain.

So, from what I have learned today, it seems as though we need to define the spectrum of densities of organisms in the sinus which can produce clinical disease, and, of course, we can look at the response in each group depending on their density of organisms.

The other point that has to do with the statistics is the improvement that has been projected with treatment versus no treatment is based on some of these earlier studies which were enriched for viral rhinosinusitis, and as Dr. Wald published in something earlier this year, maybe some of the studies that showed no effect in otitis media is because the enrollment criteria for otitis were so lax, if I am paraphrasing you correctly.

So, we may actually have a bigger effect with antibiotics, which would mean we would need fewer patients in order to show a benefit.

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DR. POWERS: John, I think one of the issues that I would like Dr. Fleming to comment on, because I think you were going in this direction before we got there, and that is that one of the reasons to try to select the patients who are most likely to have bacterial disease before you randomize is because if you randomize them and you are wrong about the percentage of people that you thought had bacterial disease, if we are only going to look at the people that have bacterial disease as part of the endpoint, you need to power the study for those people.

Suppose you thought my criteria predicts 80 percent of people with bacterial disease and you are wrong, and it comes out that 60 percent of the people had bacterial disease, and you powered the study based on 80, unless you had a bigger treatment effect than you thought, like you were saying, now you have got trouble because your study is going to end up not being able to show a difference because of a numerical phenomenon.

So, I think the reason why I was saying perhaps Dr. Gwaltney's suggested step as an intermediary is if you have a positive Gram stain, you are right, there is people that have a negative Gram stain that end up having a positive culture down the line, but it is going to be a power phenomenon, and I thought Dr. Fleming was going in that direction before we go off that.

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DR. FLEMING: I am hearing a couple of things or at least I am a little bit confused and I am still struggling to try to make sure I understand what the consensus is. Clearly, what we would like to do is identify a population as enriched as possible for bacterial infection, and in my words, I would like to do it with as noninvasive a procedure as possible because if I could it in what way, I can capture the broadest population and I know this is something that can then be broadly implemented in the real world.

However, if I have to use a sinus puncture to much more reliably capture that, then, I am persuaded that we should do so. My understanding is what I am hearing are that the conditions should be persistent symptom and a positive radiograph, and I think I am hearing the positive Gram stain that would come as a result of part of what we would learn from the sinus puncture, am I hearing that?

DR. LEGGETT: No, not from any of us.

DR. FLEMING: Okay. I would love to understand what it is, the committee consensus is for what the exact eligibility would be.

DR. LEGGETT: That is what we are wrestling with.
Jan.

DR. PATTERSON: Well, I think it is what we talked about before we got off on this Gram stain stuff,

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which is the clinical symptoms and duration of 7 days, and then the radiography and then the tap. You are going to have the tap information at least at 2 days, you are not going to have it instantly.

I think there is a lot of problems with excluding and including people based on the Gram stain. As John said, the quality can vary immensely between institutions and the people who read those things. They may not be sensitive, you might have 10^4 organisms, and not 10^5 , yet you have bacterial sinusitis with 10^4 .

As far as doing them right on the spot, most offices now, are not set up to do gram stains because of clear regulations, you can't do it in your office. You could, I guess, investigational purposes you could use it that way and have another IRB approval for doing the Gram stain for research, but I think that it is not practical and I think that we would, in terms I think maybe one of the points you are making about it being generalizable, I don't think the Gram stain would be used in routine practice even if you did a puncture.

DR. COX: Just one thing that has been hinted at, and I just wanted to sort of bring it up, and that is the issue of the number of clinical studies that we would expect, and we are talking now about having a clinical study that would have well characterized clinical entry

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criteria and also microbiologic criteria in acute bacterial sinusitis.

I think we have talked some about the number of studies here, and this actually was an issue that we did talk about previously in the March 2003 advisory committee, and in that setting where there is a broader development program and there is multiple indications within the respiratory tract, that may be a setting where, in fact, it would be appropriate to have a single well-done acute bacterial sinusitis thing, but that would be in the context of an overall drug development program that included other indications in the respiratory tract, so I just wanted to follow up on that point.

DR. CROSS: I simply wanted to echo what Jan said, that a Gram stain won't work. Aside from the CLIA regulations, that means we have had a whole generation now of physicians who are very unfamiliar with reading a Gram stain, which means it would have to get done in the main micro lab, and part of accuracy of the Gram stain, at least in terms of finding organisms is how much time you actually spend on it.

I think that it is just fraught with lots of problems and oftentimes in our hospital now, when you ask for even a STAT Gram stain, it is done at the end of the day, so you might as well just wait for your culture. So,

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it really doesn't add very much and also adds the component of missing people who do have infection, but at a lower concentration of organisms.

DR. LEGGETT: Barth.

DR. RELLER: I always learn a tremendous amount at these meetings. The Gram stains are very valuable, but they are only valuable when they are positive, neutrophils and organisms. They are not sensitive. It is the numbers that we went over.

So, to exclude people with a negative Gram stain is going to exclude those people who have 10^3 , $10^{3.5}$, 10^4 , $10^{4.5}$, when you get up to 10^5 , or whatever, then, they are more likely to be positive.

Just an aside, I think that what CLIA said, not that I agree with it, but one can't charge for a Gram stain as a provider unless you go through all the validations, et cetera. I don't think there is anything that says that one can't do a Gram stain and put that in your repertoire along with clinical things and other things to interpret how you give initial therapy on a patient, but that is just an aside.

DR. LEGGETT: In our residency treatment group of some 50 physicians, we don't even have a microscope.

Ken.

DR. BROWN: I would like to confirm that the committee has taken what was presented to us as science by Dr. Gwaltney and Dr. Powers, that we do not know that antibiotics are better than puncture and lavage and have acted upon that, and we have already decided that antibiotics are better or there is some other reason why we haven't heard about including puncture and lavage in the design of this trial.

DR. LEGGETT: Barth.

DR. RELLER: With what we have discussed, can you have that in your placebo arm?

DR. BROWN: I would love to see it there.

DR. RELLER: If everybody gets a puncture, then, the relief of pus under pressure is going to be in the placebo, and this is another reason to do it.

DR. LEGGETT: May I interject? It's quarter of 3:00 and we still have two more things to go. Let's try to keep it really focused to this and answer this first question. If we don't have a consensus, we will just say we don't have a consensus.

DR. SYDNOR: I think one important point, I think this is very important. I have the feeling people envision this study being done in some doctor's office, and his patients come in, and he enrolls them in the study. That is not the way to do it.

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There should be several sites, and there shouldn't be too many, and this should be done by investigators who know what they are doing and they advertise in the newspapers. You will never get enough patients unless you very aggressive recruit outside of a private practice.

We did these studies for years and years, and that is the only way you are going to get the patients. So, you establish the site and then you get the people and the expertise to do whatever you want. You hire somebody who knows how to do Gram stains.

I see no problem in using a Gram stain to start treatment if you have a positive Gram stain done by a competent person. That is not very hard to do. But I certainly would also enroll everybody whose cultures become positive on the next day or the day afterward, so that your patient population that's enrolled in the antibiotic trial is everybody who had a sinus aspirate culture that is positive, and there might be a few that would have a positive Gram stain, and not a positive culture, and you could argue about that, but essentially, everybody that has a positive culture would be the ones that should be enrolled.

DR. LEGGETT: Ellen.

DR. WALD: I would just like to make two comments. One is that a sinus puncture is not therapeutic. Maybe sinus lavage starts to approach therapy, but a sinus puncture is not therapeutic, it is generally designed to get the smallest amount of fluid that you can get to make a diagnosis. We are using it for diagnosis, not for therapy.

It quickly seals even if it doesn't heal, so it doesn't remain a portal of drainage. So, I don't think people should think that that is a therapeutic arm.

I would just say, too, that the Gram stain is much too stringent a criteria. It is more stringent than quantitative cultures, that we should not use it. While you can train people to do it, it is really more difficult to interpret a gram stain than to do a lot of other things, and that I think all of the patients who have fit the criteria and have undergone sinus puncture should be randomized to get treatment, you know, active drug or placebo. I don't think we should eliminate patients at that juncture.

Then, we can do an analysis on those who have a positive culture, on those who have a negative culture.

DR. LEGGETT: Tom.

DR. FLEMING: Briefly, if I am following the consensus for the eligibility. If we were, in using a sinus puncture, able to enrich the population, the fraction

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that have bacterial infections from 40 percent to, let's say, 80 percent. I had mentioned earlier that would lead us to getting a 4-fold reduction in sample size, which would be pretty profound.

But if we are putting forward criteria, which I think I am hearing, which are based on persistent symptoms and positive radiograph, but not on the sinus puncture or Gram stains, and if that, let's say, gets us to 70 percent, and hence the sinus puncture would simply get us incrementally from 70 to 80, then, that increment would only have a factor of about 1.3-fold on sample size, which is not trivial, but it is not profound.

So, I want to endorse my colleagues if they are saying we think we can get a lot of the enrichment using persistence symptoms and positive radiograph or rather procedures that I would call more noninvasive, then that has the attraction from my perspective that it is very generalizable and well defined and we may not be giving up that much in efficiency.

DR. GWALTNEY: I rarely disagree with my good colleague, Dr. Wald, but I don't see how you can justify treating patients who you know, based on the best test you have don't have an infection with antibiotics which are dangerous.

DR. WALD: I think you are not going to know that for 24 to 48 hours, and I think that you can then analyze those patients. Those patients would surely be treated today. While I agree with you as a general rule, I would not endorse treating patients with antibiotics who don't have bacterial infections, I think for the purpose of this study, it would not make sense or endear those patients to you to oust them from the trial at that juncture.

DR. GWALTNEY: I don't think a two-day delay either has any real clinical relevance or real scientific relevance. I think it would be perfectly acceptable to wait until you know your culture results.

DR. LEGGETT: Can we move on to Question 2. We have already sort of danced around this.

The strengths and limitations of placebo-controlled and non-inferiority trials. I think we are all in agreement that non-inferiority is not going to help us, it hasn't so far. I would like to hear some more specifics about the placebo-controlled versus adjunctive, therapy controlled, those sorts of statements at this point.

DR. PORETZ: As far as the placebo-controlled, if you do a study with the first company that presents a drug, and it shows that antimicrobials are of benefit in acute sinusitis, then, future studies I don't believe can have a placebo-controlled arm. Is that true?

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DR. POWERS: It depends. It depends what the magnitude of that effect is. If the magnitude of that effect is very small, say, it's 4 percent, what it turns out to be on here, we could say that that drug could be approved for sinusitis and put in the label that look, you need to realize that the benefit of this drug is only 4 percent and make your choices.

On the other hand, if you then wanted to use that 4 percent to do a future non-inferiority trial, you are talking 1 1/2, 2 percent margin and 3- 4,000 patients in that trial. It wouldn't be feasible to do a non-inferiority trial with those numbers of patients.

So, what that placebo-controlled trial actually shows will determine the future. If it comes out to be 35, 50 percent benefit, then, maybe you can select a margin for the future.

DR. LEGGETT: Janet.

DR. ELASHOFF: I just wanted to say that a study with one specific antimicrobial that comes out looking very effective can't necessarily be applied to others, and that each one has to have their own trial and the issue of whether to use a placebo or whether that one can be compared to something else, then goes on for that.

DR. LEGGETT: Ellen.

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DR. WALD: Can I ask the FDA a question. Can you insist now that some drug company take this on?

DR. POWERS: I think what we can do is we can say that there are, and what we have said, and that is why we got to this meeting, is we have said there are five ways you can do it, five potential controls in a trial, one of which is no treatment, one of which is placebo, historical control, an inactive control, or a dose-response trial.

If you want to do a non-inferiority trial, you have to justify to us what the non-inferiority margin you would pick would be. Several companies have done that and come up with the number of 12 percent. Now, from the data we presented, that number doesn't really seem scientifically justifiable.

So, that is what we are left with, and that is why we ended up here. One of things we can say is if you folks recommend it, that the Advisory Committee has recommended that perhaps doing a placebo-controlled trial-- which we almost want to get away from calling it that in that it is a superiority trial versus other symptomatic therapies.

We don't want to make it sound like we are sending these patients out onto the street with absolutely nothing and we haven't done anything for them at all, so we

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are going to highly recommend that as one of the things if that is what the committee thinks.

DR. LEGGETT: Tom.

DR. FLEMING: I would like to follow up on a couple of the comments. I think a very good question surfaced a couple minutes ago, and that is, if we did a superiority trial of some type, and that superiority trial showed positive benefit, then, would we now have a foundation upon which we could in the future then do non-inferiority trials? In principle, yes, and I think Dr. Powers' answer was on target in responding to that.

Of course, in principle, it is yes depending on the nature of the effect. The criteria in the ICH guidelines have been formulated as guiding when you can do an non-inferiority trial. It is when you have an active comparator that has substantial efficacy, that is precisely estimated in a context that can be generalized to the setting in which you are going to do your non-inferiority trial.

So, if we show in placebo controlled or some other superiority trial a 30 percent improvement with precision in that estimate, absolutely, we now have a basis in the future for doing a non-inferiority comparison plus clinically, that is exactly when you would want to do it.

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You wouldn't want to then continue to use placebo if you have a profound effect.

On the other hand, if it's positive, but it is really a trivial effect, then, as Dr. Powers points out, you have violated the principle of having substantial efficacy, but I wouldn't even want to do a non-inferiority trial in that setting. It is just a trivial difference.

Yes, it would take an infinite sample size to rule out a trivial inferiority, but it wouldn't be a setting where we would be compelled to anyway, so the exact setting in which clinically and ethically you would want to follow up with a non-inferiority trial is exactly when we could.

The reason that it is difficult to do so now is that we don't have the past history of these types of studies. We have got to start at some point. If we start at this point, we will have the foundation for doing so in the future.

Now, what does that mean we have to do now, do we have to do placebo? I would say what we have to do is a superiority trial. Now, a placebo is one obvious way to do that. There are other options. You could look at comparison of experimental to standard, and just hope you are superior.

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Well, if you were, that would be enough as long as you could believe the standard wasn't harmful. You could do a dose-response and that would be also sufficient although there is a risk for a false negative there, and that is if the lower dose carries a lot of the benefit, you may not be able to see the benefit.

You could do a standard plus experimental against standard, and if that is superior, that also is the evidence you would need, although that would only make sense if it was clinically sensible to add on your experimental to the standard.

So, for all of these reasons, there are a lot of settings where I think the obvious superiority would be a placebo, and I completely agree with Dr. Powers in that setting. I think the term "placebo" is often misunderstood. It gives the sense that the control arm isn't getting anything, and that's not true.

We should be delivering to the control arm, standard state-of-the-art implementation of standard of care, so symptomatic therapy at whatever it would be at state-of-the-art against which we would be adding this experimental intervention for which there hasn't as yet been proven efficacy.

In so many areas in clinical trials, patients on both arms are benefitted because you are achieving a higher

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level of standard of care and a higher level of attention and management in a clinical trial. So, those patients, even if they are on the standard of care symptomatic management, with the additional care they are getting, tend to do better than not being part of the trial.

So, the concept of being randomized to a placebo, I think is often misleading as to what the control arm is really getting.

DR. LEGGETT: Could I take the liberty of asking if there is general consensus from this committee that we do not believe a 4 percent imprecise improvement is significant? Does anyone disagree with that? Ellen.

DR. WALD: Could we just discuss adjunctive therapy for a moment, because I don't think there is a standard adjunctive therapy, and I wouldn't specifically endorse its use as an alternative arm.

I think there is very little evidence, less and worse evidence than we have for antibiotics, and I think giving patients multiple medications sometimes makes their adherence less good, so I have, as a rule, not used them when I think that my antibiotic is my potent treatment piece. I would be interested in other opinions.

DR. LEGGETT: I think I would be happy either with decongestants or without.

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DR. POWERS: Could I ask Peter Starke from the Pulmonary Division to address some of this because our Division met with the Pulmonary Division to address this question just a while back.

DR. STARKE: Good afternoon. First of all, I should say I am a pediatrician, so that is my background.

To my knowledge, there are no adjunctive therapies that are approved for sinusitis at this time, however, I would say that you can't very well get away with not treating patients for pain. So, if they have pain, headache, sinus pressure, and I use that in the general term of pain, not in terms of sinus disease, but pain somewhere in the facial area, you can't help but treat that pain.

I think that is the basic therapy that one would give as you start to get into other therapies, for example, any intranasal therapies, first of all, I am not sure that it gets into the sinus, as has been pointed out, but it may be treating other disease that is comorbid disease, and one of the things that you haven't talked about that I would be interested in hearing about is allergic disease.

I think that you have been good in terms of the way you have been separating out the terminology here, acute bacterial sinusitis from rhinosinusitis, because the allergists that we hear from would like to combine the

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terminology and call acute rhinosinusitis, the problem there being that it dilutes what is actually bacterial disease and what we want to think of as bacterial disease, acute bacterial disease with other etiologies.

As you all know, acute rhinosinusitis is usually viral in nature, but we have a large proportion of patients with sinus disease who also have allergies, so that is the second condition that may require co-administration of medications.

I would suggest the way we think of it is that once you have gotten through this first level of enrollment, that one actually has to think about whether any patients who are on other medications for allergies, they have to be balanced within the groups and you have to look at outcomes based on that, as well.

So, certainly patients who have allergies, you wouldn't stop their medication, but you are going to have to balance it out.

DR. POWERS: I think what matters to us is not which adjunctive treatments they receive, but that it is standardized across the arms of the trial. When you look back at some of placebo-controlled trials, it is at the investigator's discretion of who gets what, and I think that is what becomes problematic because if that is imbalanced between the arms, then, if there are treatment

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effects that we don't know about for these adjunctive therapies, then, we can't figure out what it means.

DR. STARKE: Presumably, the randomization process helps to balance out those things, but you would need to look at efficacy for each subgroup, particularly for allergic versus non-allergic disease.

DR. LEGGETT: Ellen.

DR. WALD: For purposes of a trial, and our upper bound of symptoms being 28 days, is we are trying to avoid including in this study group, patients with allergic disease, and if people were on that kind of medication, I would say that would be an exclusion characteristic, because it is going to be hard enough as is.

DR. LEGGETT: Would you accept the use of non-inflammatory agent and hope you had balance?

DR. WALD: You mean for pain?

DR. LEGGETT: Yes.

DR. WALD: I agree with John, I think whatever you do, you do across both sides, and you could make it PRN and then use that as an outcome, as well, you know, who stops needing pain medication faster in the antibiotic versus placebo or comparator.

DR. LEGGETT: Good point.

Tom.

DR. FLEMING: Just on that point, we have to remember what randomization does and doesn't do for us. Randomization gives us comparability at baseline, at least it eliminates systematically occurring imbalances. Randomly occurring imbalances can exist in smaller sample sizes.

But it doesn't influence, of course, what might be differential needs for ancillary care post-baseline if the intervention that we are randomizing to actually is influencing outcome.

So, if the antibiotic is effective in reducing symptoms including pain, then, it could be systematically emerging over the course of time that the control arm needs more pain medication, which is, in fact, one of the results of the intervention. The intervention is reducing the need for as much pain medication.

DR. LEGGETT: Ed, how do you feel about this discussion so far about placebo and non-inferiority, and can we move on?

DR. COX: I think we have covered the issues for the first bullet.

DR. LEGGETT: What is the thing about comparative microbiologic data?

DR. COX: I think we touched on that some in the discussion of the first question, and that deals with the

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current guidance document which recommends a clinical trial followed by a microbiologic-driven study.

I think we have touched on that some in discussing how a clinical study highly characterizes the patients clinically, and that also includes rigorous microbiologic evaluation, may be able to serve that role.

In the setting of broader development program, that study, if well done, is sufficiently large and there is a broad range of indications, that may be a study that could support acute bacterial sinusitis. I think we have covered that issue of the comparative microbiologic study.

DR. LEGGETT: So, after Tom's question, we will move on to point 3?

DR. COX: I think that sounds good.

DR. FLEMING: I promise to keep this comment brief.

There was just one issue raised in the implementation of placebo-controlled trial that I would like to comment on, and that is might we have cross-ins occurring at some point. Let me just say if they are very infrequent in occurrence, I am not so worried, but if we wrote into the protocol, for example, that after a given number of days, there isn't resolution, then, we would cross-in, and we would define those people to be failures at that point.

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I think it is important to realize that a very non-trivial bias could emerge. So, for example, suppose that in a true placebo, there would be 50 percent resolution at day 3 and 70 percent resolution at day 10, so it goes from 50 to 70.

Let's say the antimicrobial intervention is a placebo, it doesn't provide any benefit. We would see 50 at day 3 and 70 at day 10. Now, in the control arm, if we randomized in the patients to the control arm, if the 50 percent, there will be 50 percent resolved at day 3, if the other 50 are crossed-in, because they haven't resolved at day 3, and we call them failures, then, we are imputing failure for all time, so you would have 50 percent resolution at day 3 and still only 50 percent resolution at day 10, so we would see a 50 versus 70 difference in a truly indurate agent purely because of the bias that we induced by calling somebody failure when they crossed over.

DR. WALD: Wouldn't the same thing happen in both groups?

DR. FLEMING: It would, but only if you would call, then, those on the microbic side when you are crossing them over, so you are going to cross over the microbic sides to microbic side as well?

DR. WALD: I wouldn't call them crossovers, you just have patients who failed therapy for whatever reason,

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in whichever group. You are blinded, you don't know, and what you probably would have is an alternative antimicrobial as your fail-safe, so patients who were getting an antibiotic and failing it, now are getting another one, patients who were getting placebo are now getting an antibiotic, and you don't have to know who they are.

DR. FLEMING: But even if you do this, what you are presuming is that what will occur beyond that point, in fact, would not have been influenced by the microbicide, so let's suppose that, just to change the example, then, let's suppose that the microbicide is effective in leading to an enhanced resolution, but it is particularly evident when you look at it over a longer period of time than just over the first few days.

Then, by imputing failure, then, you would not be underestimating or not fully capturing the benefit. The fact of the matter is some of these people will resolve if you continue to follow them even if they haven't resolved early, and so imputing failure, whether you are doing so equally at day 3, in the microbicide and the control arm, still could be giving bias.

My own sense the outcome should be assessed as it actually occurs in all patients, at day 3 up to day 10.

Let's say you have defined day 10 to be the final day of

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your follow-up, then, I don't mind if you crossed them over after that because you are not influencing the assessment of the outcome.

But the bottom line is you should be assessing the outcome on all patients until the date at which you have defined the final period of follow-up to avoid any biases, and if the cross-ins are fairly minimal, you are going to have only a minimal diluting.

DR. POWERS: I think what Dr. Fleming is getting at, I think from the clinical point of view, is it depends upon what the natural history of the disease is and how you would expect that to occur in the placebo arm.

Unfortunately, that is one of the pieces of the pie that is missing in this disease, is we don't know what that is. Dr. Wald, you had said earlier that we expect antimicrobials to work in 48 to 72 hours, but that is what we are trying to measure in this trial, would be how long does that take.

We know the antibacterial effects probably occur at that point because Dr. Anon's data there showed that we can track over time. What we don't know is how does the clinical symptoms impact, and if you look at just those four patients that Dr. Anon showed, it looked like there was a lag time of maybe two days beyond when the organism was gone and the symptoms resolved. So, we need to know.

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I think the danger here is putting that early escape thing too early in the course of this illness.

DR. WALD: I would just say that in clinical practice, 72 hours, if your patient is not improved, you do something as a clinician. That is the time point whether you have otitis media, acute sinusitis, or acute pneumonia. If you are not somewhat better by 72 hours, you check your diagnosis, if it's correct, you change your drug.

DR. LEGGETT: That is how a clinical trial is different from clinical practice.

DR. WALD: But if you are using placebo here, a non-active comparator, that you have to promise patients something, at least that would be important to me as someone to sign up for this.

DR. POWERS: Let's take another disease where know antimicrobials have very little effect, like secondary acute infections of acute bronchitis.

We know that at 2 weeks, about 40 percent of those people are still coughing, and at 4 weeks, about 20 percent of those people are still coughing. If you considered at 2 weeks that those people were failures and you switched them all over to antimicrobials, it could look like antimicrobials had a big effect, when, in fact, they don't.

So I think that is why we need to know what the natural history of the illness is to pick that time point. I understand, as Dr. Leggett said, the issue for us is that is fine what clinicians want to do in clinical practice, and we are not trying to tell them not to, but in the terms of this kind of a clinical trial, we have to be careful about placing that time point too early for the escape.

DR. COX: Dr. Leggett, before we completely leave Question 2, just hearing some of the additional comments, I am wondering if we can just get a little more clarity on placebo-controlled studies and comfort level because we have talked about two different groups here with the persistent group the urgent group.

I am just wondering if we can get a little more feel from the committee members with regards to the setting of placebo-controlled studies and people's comfort level there.

DR. LEGGETT: Listening to Ellen and Jack, I get the feeling that people would not be quite so comfortable in the urgent setting in less than 7 days, but may be comfortable with 7 days or longer.

DR. COX: Thank you.

DR. GWALTNEY: Well, I would just like to say that if you have a treatment--this is a general statement and it is very obvious, but I think we tend to forget it

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particularly in current times--if you have a treatment and you don't know if it works, one thing you can be sure is it is going to have side effects, because I don't know any medicine that doesn't have side effects, and so if you have a disease, and you take a treatment which doesn't work, then, the odds are that something bad is going to happen to you rather than something good, and antimicrobial agents do cause toxic epidermal necrosis and anaphylaxis.

When you have seen one or two of those patients, it is very impressive. It is rare, but it is impressive, so if you are in a trial, I think the investigators and the subjects need to realize that it is not always that it does good, you know, it is very obvious, but we tend to forget that.

DR. LEGGETT: Mark.

DR. GOLDBERGER: Just to follow up on the last couple of comments, then, I take it you have seen the patient population that was defined a moment ago, perhaps less rapidly progressive, more than 7 days of illness. Most people here feel a protocol could be developed that would get, for instance, through their IRBs, because realistically, you know, when we deal with pharmaceutical company, and if we are pushing fairly strongly in a certain design, we have to realistically be comfortable that what

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we are telling them we think they should do, they will be able to go out and reasonably implement them.

It is helpful sometimes to get some feedback from people who are closer to those issues than, for instance, we are.

DR. LEGGETT: Keith.

DR. RODVOLD: Being a past member on IRBs, as well as doing a lot of trials, I think that you are going to run into the problem of that. There is going to be about 50 percent of IRBs are going to be uncomfortable with placebo no matter what kind of study you put up, and that already goes on.

The other aspect of it in the groups that will let you go through an IRB with a placebo trial, I think you are going to have to have a rescue for that arm, and I don't think, in the beginning, you are going to be able to double randomize, randomize them back again.

I think you are going to come down to some critical point in time, and that is where Ellen's comment about clinical practice is 72 hours is when you would make another call, IRBs are loaded with people that are practitioners, as well as academic people, and some IRBs are totally more practical people than academic people.

I think they are going to demand, at least in the early trials if you launch these, that you are going to

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have to rescue them at day X, and that day X will probably be clinical practice experiences versus trial experiences.

I agree with Jack's comment about limiting this to the really selective centers that have great experiences and good, highly-trained people, but their IRBs will still get in the way a little bit, so those are some practical issues as a past IRB members, as well as a trial person that I think come to play after all this academic conversation.

DR. LEGGETT: Jan.

DR. PATTERSON: I think I might frame it a little bit differently and say sinus aspirate and adjunctive therapy compared to sinus aspirate, adjunctive therapy and antibiotics instead of saying the term placebo.

Ellen says it is not that the aspirate itself is not therapeutic, but the adjunctive therapy may help and taking some of the pressure off may help at least symptomatically acutely.

I think you could frame it, is it really truly placebo if you are doing those other things? I think you could frame it a little bit differently.

DR. POWERS: I think that is one of the points I wanted to raise. Before I came to the FDA, having been an IRB member myself and being a clinical investigator, one of the things I thought is when you go an IRB, you are

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presenting your case of why you think this trial is worthwhile to the IRB, not presuming the IRB knows everything about this disease.

One of the things that we really discovered looking through these 14 placebo-controlled trials, I mean when I started this out I said, okay, we will find out what the number is, we will pick the number, and we will go forward with an non-inferiority trial.

It is surprising to me of what we found, and I don't think most IRBs would know that that is the case. So, I think part of it is picking investigators who would present that case in a cogent way to their IRB.

DR. LEGGETT: Moving on to Question 3. Discuss the issues of measuring outcomes in patients in trials of acute bacterial sinusitis.

I assume the outcomes we are going to be measuring are, in part, the symptoms and signs that got us into the trial, and then return to daily activity.

Ellen, what other things can you think of off the top of your head that we would want to measure as an outcome?

DR. WALD: I think those are the things. You just try to say when nasal congestion has resolved, nasal discharge has resolved, cough has resolved, sleep has

returned, appetite has returned, activity has returned, so it is a composite of those real-life issues.

I would again say, though, that there are certainly at least some parents, I don't know about adult patients, who won't say they are completely well, so you may not get to baseline, you know, they just have some minor residual symptom that will keep them from saying they are entirely well, and I don't like to hold that against my study drug. So, you need a way out of that, I think.

DR. LEGGETT: Jack, anything to add?

DR. GWALTNEY: Well, I think it really is an advantage to do quantitative bacterial cultures, because there you are dealing with interval data, they are in increments of log to the base 10, so you don't need very large sample sizes in order to look for differences in bacterial titers in your different groups.

So, I think that is a great advantage to doing, not just semiquantitative, but quantitative cultures, which aren't a big deal, you just do the dilutions and plate those things out.

Certainly, your sample size is a much smaller for dealing with those kind of data than with the clinical data, which are just ordinal and which have much larger variance.

DR. LEGGETT: John.

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DR. BRADLEY: In the clinical trial design, with some other diseases, we have discussed the difference between primary, co-primary, and secondary endpoints and having microbiologic endpoints versus clinical endpoints and actually having a different delta if it's a non-inferiority trial with a microbiologic endpoint as opposed to a clinical endpoint, so it gets very complicated very quickly.

I will go back to the FDA and sort of throw it to you. How would you see endpoint evaluations because we have talked about clinical scores, Kaplan-Meier plots of time-to-resolution of symptoms have been presented, and then now we will have some microbiology hopefully that will allow us a micro endpoint, which could be more precisely defined.

DR. POWERS: What we don't want to do is we don't want to separate out analyzing microbiologic outcomes and analyzing clinical outcomes without linking them to the individual patient especially in a disease--one might think that is more appropriate in a disease like meningitis where we are more certain of that association.

Here, what we have presented today is we are completely uncertain of that association. What we have been trying to look for other diseases like exacerbations of chronic bronchitis falls exactly into this idea of

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symptoms, and there, the microbiology, who knows what it actually means. So, we have been working towards things like patient diaries and coming up with some kind of scale very similar to what was done in the influenza trials.

That takes a lot of work, but we are actually trying to do that or get it started and then maybe get somebody at the IDSA interested in this to take it forwards, because we want that kind of scale to be available to everybody if we can get that moving.

DR. LEGGETT: Very good idea.

Janet.

DR. ELASHOFF: With respect to time of resolution of symptoms as a way to talk about an endpoint, so that then you are doing a Kaplan-Meier analysis, like any outcome that you might talk about, it has its pros and its cons.

I just wanted to mention a couple of specific issues. One is that in the past, it seems that the clinical cure has been defined at a physician visit, essentially by the physician interviewing the patient.

To talk about time to resolution of symptoms, you would have to have it done every day with some kind of patient diary, hopefully, something electronic, or maybe even people calling up on the telephone and punching 1, 2,

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3, 4, or 5 for each symptom or something like that because paper diaries are notoriously problematic.

I wanted to mention, though, something that one has to think about in looking forward. For placebo-controlled trial, there is no real problem with time to resolution as an outcome, but if you saw a really high effectiveness of some antibiotic and now, in the future you want to use a non-inferiority trial with this same outcome, defining non-inferiority margins for time to resolution can be extremely problematic especially if the hazard ratios over time are not constant. It may not at all be clear how to define such a non-inferiority margin.

So, if one is going that way and thinks that you would ever do non-inferiority trials in the future, you need to be proactively thinking about how to deal with that.

DR. LEGGETT: Would it be statistically valid to come up with a fixed endpoint once you knew where it was supposed to be from this first trial, so in the future, none of your early trials, you have a fixed endpoint?

DR. ELASHOFF: It might be reasonable although I would guess that that sort of thing would shift around with your populations, just everything else seems to shift around.

DR. LEGGETT: Joan.

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DR. HILTON: My comments were on a related topic. I was concerned about how frequently the endpoint was going to be measured because if you do want to do time to resolution, you have to have frequent measurements, over time, and I wondered what the total duration of the follow-up time is meant to be.

Finally, it seems to me that if we do a time to event type analysis, then, when a subject fails on one arm, we stop following them, so whether they have a rescue or escape therapy afterwards, that information wouldn't enter into the analysis. So, that would be one complication removed if we went with that type of an outcome analysis.

DR. LEGGETT: So, you are saying we could have a rescue if we did the time to resolution?

DR. HILTON: But that requires you to be able to assess the outcome repeatedly and accurately, so I wondered if Janet's idea was one of the feasible options or if you have figured out how you would do that.

DR. POWERS: I think what we are using as a model here is something Dr. Cross pointed out a couple of hours ago, and that is the influenza trials. The symptoms of that disease are very similar to acute sinusitis. The way those trials were done showed a difference for influenza

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drugs, so it would seem like a good model, and the way that was done was twice daily, patient diaries.

DR. LEGGETT: Alan.

DR. CROSS: It seems that one of the things we addressed earlier is trying to tie in the microbiologic resolution with the symptoms, and so far we have talked about getting a puncture at study entry.

I guess short of doing what Dr. Anon has done, which I think might be heard to do on the whole population in the study, how can we actually expect to tie in the microbiologic resolution with the clinical outcome?

DR. LEGGETT: And another practical complication other than the second sinus tap, if it's resolved at the time that you do that second tap, you are not going to get anything.

Barth.

DR. RELLER: The taps are, to me, crucial for enrollment. I am not sure they are at all important as a second tap down the line with the emphasis--I mean we already have discussed that there is, from what we know, not a clear relationship between cessation particularly if the second tap is done anywhere near to where the antibiotic is or certainly not on antibiotic that it is going to yield any information, so if there is not a clear--Dr. Fleming went over it, it can't be used as a surrogate

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because it doesn't correlate well with resolution of symptoms.

What we want is do they have the disease or not, for which we absolutely need microbiology. What we need for resolution of symptoms is what has been discussed, like in the influenza trial. So, I would put the emphasis on the first tap and scrap the second tap unless, in contrast to the reality currently, where people have failed and the persist in being symptomatic, then, I think, well, would like to see a tap, is to require a tap if somebody is registered, they still have a positive radiograph, and they are the same or getting worse after therapy.

What do you think about that, Dr. Wald, of a second tap if they are going to be a failure and they are worse?

DR. LEGGETT: Wouldn't that be a different trial? Wouldn't, in that trial, we are trying to figure out that we could use a surrogate marker? I don't think that is the purpose of this trial, but go ahead, Ellen.

DR. WALD: I guess you could draw the analogy to acute otitis media. I think that is where you are trying to learn, you know, why did the patient fail, was it a bug-drug problem, or, you know, once in a while patients do fail clinically just because they need that sinus

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ventilated. It doesn't happen very often, but it can be the results.

I think you are just trying to learn stuff from that second tap. If the patient agreed, I think it would be fabulous.

DR. WALD: John.

DR. POWERS: We have noticed--there is one NDA we didn't present because we wanted to look at this before-- but one NDA did do sinus punctures before and after, and we noticed a pretty poor correlation actually between the clinical outcomes and the microbiological, and one thing struck us, and that is that what may also impact on this is the quantity of organisms at baseline, which we don't know, so if you only tap the failures, and those people have a particular organism present, is it because that drug isn't effective for that particular organism, or because those people started up at here, at a higher level, and everybody else started down here?

Without the quantitation to assess that, it is very hard to make any comments about drug efficacy versus some baseline parameter that you didn't know, like the quantitation of the organisms.

HIV trials have it down. You have got viral load, and if you drop 2 logs, even if though you are not

suppressed, that is considered a success, and we don't do that in bacterial trials, so it is hard to know.

DR. LEGGETT: I would like to echo something that Barth said. We are not going to create the perfect trial here.

DR. POWERS: I think our concern is that what we see, I can see someone taking Dr. Anon's data and telling us, look, our drug makes the bug go away faster, therefore, we want to get labeled as better than that guy's drug, and that is what concerns us about that because we don't know whether making the organism go away faster, what it means clinically.

We also don't know even in the setting of a clinical trial whether that means that those people had more bugs than the other guys did at baseline.

DR. RELLER: I am more interested in the second tap, if it were done to see if the organism is resistant to the drug used, because I think one thing that has actually not been discussed in the context at all is what is resistance in terms of these major pathogens, the putative pathogens, the recognized pathogens for the treatment of sinusitis.

There has been a lot of discussion of drugs, penicillin-resistant pneumococci, drugs that would, by some criteria, be called inactive, but they work anyway, and I

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think we don't know that information for bacterial sinusitis.

That is my interest in the second tap, for those people who don't get better. If they get better, we will know what susceptibility is on the first one.

DR. LEGGETT: We are going to let the FDA determine when to do that.

DR. POWERS: That is the problem with interpreting this. If you only tapped the failures, you still can't tell what it means as far as interpreting antimicrobial resistance. I don't want to get into this one NDA, but the one we looked at, 21 people had a second positive culture.

Everybody got tapped, it was 100 and some patients, everybody got a baseline and a follow-up tap. The follow-up tap was done at day 10 or so, not on therapy at the end.

Of the 21 people that still had a positive culture, all 21 were clinically cured. So, to be able to evaluate what resistance means, you need to tap the successes, as well as the failures, because the presence or absence of the organism here, it is how it correlates clinically that means something.

So, in other words, clinical guidelines suggest amoxicillin for this disease. If we know that you are

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going to get better no matter what drug you get on day 7, so, it may be that your amoxicillin-resistant Strep pneumo is still in your sinus, but you are better, so correlating those things requires looking at the people who are successes, as well as failures, to be able to make that distinction.

DR. LEGGETT: John.

DR. BRADLEY: Earlier, I mentioned about the difficulties in doing these double tap studies for otitis, you tap them on entry because they have symptoms and then you tap them three to five days into their treatment, and some of those centers are now trying to do quantitative cultures on those ear taps, which I think plays perfectly with what you said.

I was unable to get any parent talked into a double tap study despite the fact that we offered conscious sedation for them, however, that is not to say that other studies didn't collect the data, and that I don't use those data in figuring out whether an antibiotic works or not.

So, the concept that a world wide study could potentially be set up with sites where multiple taps would be reasonable seems to be a logical way to collect all of this valuable microbiologic data that you both are asking for.

I would ask Dr. Gwaltney and Dr. Sydnor if they have done a multiple tap study, if it would be feasible to do this with the current feeling of how people view antibiotic therapy, the public.

DR. LEGGETT: Dr. Gwaltney.

DR. GWALTNEY: I showed you a slide that went from 1979 to 1997. Those were all double tap studies. We have not done one double tap study, we have done a dozen double tap studies. I can't remember the total number of patients, but it is in the hundreds, so they can be done.

But I personally like the idea of leaving the indwelling catheter in there, the way Dr. Anon described, because you don't have to do the second tap, not that it can't be done, we did it for years and years, and I think we could do it tomorrow, although we are not doing it anymore, so I am not looking for business, we are through, but I think it could be done in the United States.

There is I think a very nice aspect of leaving the catheter in because then you are seeing the cultures over time, and it doesn't appear to be a very long time before the infection is eradicated and you have got the quantitative cultures and the clinical material, the x-ray, everything to quantitate with the evidence of infection.

And this is an infectious disease and we really need to know if we are doing something about the infection.

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DR. LEGGETT: Ellen.

DR. WALD: You wouldn't need to have that many of those kinds of patients in whom serial data were available to learn when we should do a second tap if we wanted to only approach it that way.

DR. POWERS: I think that would be a useful approach. It is kind of like getting two taps with actually only one tap, but getting multiple time points along the way. One of the things I think we would want to see though is that same material after the drug is gone from the body to see if there any kind of relapse, because that gets to this question of are we just measuring suppression or is that organism truly gone.

DR. LEGGETT: Ed, are we just about finished or what things have we not touched on?

DR. COX: I just had a question I thought maybe Dr. Gwaltney might address. I am just thinking about the catheter going in and the issue of, say, for instance, a drain or a catheter, and the initial culture might be sort of the cleanest sample, if you will, but after the device has been in place for a while, the issues of will that culture represent, in part, what is in the catheter.

Would that be an issue, too, of potential concern here with the follow-up culture?

DR. GWALTNEY: I think that is a good question. I think the answer is no. The reason is I am certain that material gets into the sinus all the time. We know when you blow your nose, you get it in there, and the sinus, for whatever reasons including the mucociliary escalator and probably nitric oxide and other things fights that continuous contamination that gets in there.

I think if you have catheter in situ, in the artificial situation. The sinus is still doing its thing, so theoretically, I think there is good reason to think the sinus is still going to do all right in spite of the fact the catheter is there, but more importantly, at least we have a little bit of information on 4 patients, and the sinus became sterile. They were just culturing for pneumococci, they were culturing for bacteria, and it became sterile.

So, I can't say with assurance that would happen with more patients, but it is so easy to find out. This is such a doable experiment from which we would learn so much new important information. That is why I find it very desirable or very attractive.

DR. LEGGETT: Barth, Tom.

DR. RELER: I want to come back to John's comment. It seems to me that the greatest information we are going to get for resolution of organisms related to

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their susceptibility is the detailed clinical follow-up relative to the organism that was present and having that bacteriology on everybody in the first place.

I don't think a second tap is--I understand what you are saying, but I mean we are going to get that information, which brings to a question that in relation to this second tap, which I am not advocating routinely because I think it makes it far more complex than the good that we would lose by emphasizing getting people the first time.

But, Dr. Gwaltney, in the studies where you did do a second tap, and given these dramatic pressure and what happens, is there a phenomenon in those persons, for whatever reason don't resolve, who get a superinfection after initial antibiotic, or does that just not occur clinically?

DR. GWALTNEY: We don't have a lot of information on that, but people who don't respond to initial therapy and end up getting a sinus aspirate culture--and my wife was one of these, she went through this whole thing--when they get the sinus aspirate culture, most often you don't grow anything, and that is quite puzzling, but that is not always true, but as far as what has been published and what I am aware of, you don't find some resistant pneumococci or some unusual bug or something like that.

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I mean you would think that would be the case. That is not so. So, some people now think, and certainly is a reasonable hypothesis, that chronic sinus disease in these patients that don't recover from the acute infection is something else. Maybe there is something wrong in the immune system of those people, but despite what I originally thought would happen, retap these failures, you don't find anything that really explains what is going on.

DR. RELLER: That is useful information in terms of our understanding.

DR. GWALTNEY: Yes.

DR. LEGGETT: Tom.

DR. FLEMING: I have an overall comment relative to Question 3, so I am happy to defer and wait for other discussions on retap, is there more discussion of this?

DR. LEGGETT: I hope not.

DR. COX: I have heard a couple of folks talking about retapping in the setting of failure, and we have discussed 2 in part, but I was wondering if we could just get a little more feel from the committee about just retapping in the absence of failure. I am not hearing much in favor of that.

DR. LEGGETT: I don't sense a consensus opinion about why we would do it, what it would show. I think everybody, maybe it's because there is not a lot of data in

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addition to some theoretical issues, leave it open to folks.

DR. BRADLEY: I think there is valuable information on the natural history of the disease to retap all of those who are culture positive at the first tap, all of them, whether they respond clinically or not, just as we learned in otitis media. So, that is my vote, and I know that there are probably people who disagree with that.

DR. LEGGETT: Whoever would like to speak up is fine.

DR. SUMAYA: I would think that a retap would be very useful again more from the natural history of the disease. Nonetheless, I think I would try to limit it in this particular study to those that relate to failures.

DR. LEGGETT: Jan.

DR. PATTERSON: I don't really think I would favor a retap except in the case of failure although if you had a center that really could do double tap studies, it might be useful to have it done in that one center for the natural history of disease.

DR. CROSS: I agree, I think it would be nice to have, but it would be a very hard sell.

DR. LEGGETT: Ellen.

DR. WALD: I would like to learn as much as we could from those indwelling catheter studies, and not

insist on a second tape unless there was a clinical failure, and then if it was possible, do it.

DR. LEGGETT: That is essentially my feeling.

DR. RELLER: I agree with the two of you.

DR. PORETZ: I would tend to agree. Dr. Gwaltney has done it for years. Although that new catheter is fascinating and I think if you could make use of that, that would be a major plus.

DR. LEGGETT: John.

DR. POWERS: I did a poor job of explaining what I was trying to say to Dr. Reller earlier. I think if you want to look at the letter we wrote in the Peds ID journal, in this month's journal, what we did for otitis media was we made a 2 by 2 table, and we took clinical success yes/no, positive culture on the second tape yes/no, so you need to have the yes part of clinical success to fill out that cell of the 2 by 2 table to evaluate this correlation.

If you only tap failures, you only got 2 of those 4 cells. It is therefore very difficult to evaluate the impact if antimicrobial-resistant organisms if you can't fill out the other two cells of that 2 by 2 table.

That is where I think the utility of doing follow-up sinus punctures on all people comes from. It would probably be impossible if you had to do two taps, but that is where I think the idea of this kind of leaving the

catheter in becomes very attractive because the patient goes home, comes back, and really don't need a second procedure, just has to get the sampling done.

DR. LEGGETT: As long as we could get everybody to guy the SinoJect.

DR. CROSS: I had a question for either Ed or John. Earlier, in other meetings we have talked about the need for either one study or two studies.

I guess the import of what we have been discussing here is that if we get one rigorous, high-quality study in which we have both microbiology and good clinical design, that that would be adequate for going forward for an NDA?

DR. LEGGETT: I though that was in the setting of we are also looking at community-acquired pneumonia, looking at otitis, and looking at a bunch of other stuff, so there would be an aggregate of data. If they only were going for acute bacterial sinusitis, my vote would be no, two trials.

DR. COX: That is consistent with what we talked about in the March 2003 Advisory Committee. In the setting of a well done, adequate and well-controlled study of acute bacterial sinusitis, good clinical and microbiologic characterization in the setting of an overall program with other indications that do provide evidence that the drug

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works well in the treatment of respiratory tract infections, other indications, some of which may be more serious infections, then, in that setting, it may be appropriate to consider one well-done acute bacterial sinusitis study, but in the instance of where those other indications aren't there to provide support to the acute bacterial sinusitis indication, then I think we would be looking at more conventional 2-study approach.

In that setting, certainly, well-done studies would provide more compelling evidence of the drug's efficacy.

In addition to, you know, in this setting where a more narrow program is being pursued, a more limited number of indications, we need to also get sufficient number of patient exposures in order to gather the safety data that we need also.

DR. LEGGETT: Keith.

DR. RODVOLD: In regards to the double tap, one of the things I would say about his studies that he is doing I think is also important, it has been discussed and we made a lot of decisions, is that I think you need to characterize from drug family to drug family, cidal versus static drugs, drugs that penetrate well, don't penetrate, and by doing his studies in small pilots with different groups, I think that would sort out for you maybe when to

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do a double tap with which type of compound that is in study at this point.

Without doing more work and going across drug families with protein binding issues and all kinds of other pharmacological characteristics, and just stamp this thing at this point.

I think there is a little bit of concern about that from my perspective, too, in all these trials, that if you do one placebo study with the fluoroquinolones, that is applicable across the boardwalk, too, I think that is a little concerning to me, so I think you are going to have to go through a few iterations of this, both of his trials, but also a placebo trial with different families to make sure it holds up across.

Pharmacologically, there are lots of different drugs here.

DR. LEGGETT: If we did need a good superiority trial, though, it would put us not in a position of the azithromycin in otitis situation.

DR. FLEMING: Let me give an overall comment relative to Question 3 and try to tie in some of the other issues that were raised.

I would surely endorse what I think many have said, in fact, I think all have said, and that is the

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endpoints that we would need to assess would be both clinical endpoints and microbiological endpoints.

In the absence of having a truly validated surrogate for the clinical endpoints, I would argue that the clinical endpoint of resolution should be the primary endpoint, microbiologic endpoints would be very important secondary measures.

As it relates to the formulation of this primary clinical endpoint, in principle, given that we are looking for measures that are sensitive and clinically relevant, I could see either a fixed time assessment or a time-to-event analysis as being appropriate.

My concern with the fixed time is I wouldn't want it to be too early because fixed time early ignores all of the information after that, and in a self-resolving disease setting, I wouldn't want it to be too late, because a lot of the signal could be earlier, and that is the reason that I would be very interested in pursuing the time to event.

I think what Dr. Powers has indicated as a possible model is something important to think about. Whether it's fixed time or time to event, I think it is going to be important to have validated measures that we are going to be using, so I think the concept of following on what's spent on influenza and traveler's diarrhea,

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looking at twice daily, patient diaries validated is I think a very interesting concept.

As has been pointed out, time to event does give you a big more efficiency and power, but you get what you pay for. It does require more information, so it is going to require something like this that has more frequent assessments.

My final comment is clearly, when this study is done, it will not only serve the purpose of giving us insights about benefit-to-risk of this antimicrobial, but hopefully it works toward setting the stage for design of future trials and potentially allowing us to do comparative studies and potentially non-inferiority trials.

It is going to be tempting and in fact relevant to explore the data and find out whether time to event was most sensitive or would it have been more sensitive to look at fixed time at day 3 or day 7 or day 14.

That is certainly relevant to do, but I would just caution against a strategy that would say post hoc, we will take whichever one of those was the most significant, fix that as the established effect for a future non-inferiority because we have something called regression to the mean, and that is, if you look at multiple point in time, one time may show up as more striking, but that may be more randomness that it looked better at day 5 than it

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did at day 7, so fixing in the future a non-inferiority margin based on what appear to be the most striking difference is at risk of a regression to the mean.

You are overestimating the true effect at that one particular time point. So, yes, we can explore, but we have to be very cautious not be overinterpreting noise in the data as well.

DR. LEGGETT: Any final comment by anybody except Ed or John or one of you guys?

DR. POWERS: I had one comment, it had nothing to do with the scientific discussion. I think from looking at all these discussions today, you can see how much work all the FDA staff put into accumulating all of this data, and I wanted to thank all the medical officers that actually did a lot of this work in pulling all of this information together, because I learned a ton doing this.

I also wanted to thank the statistical staff, Dr. Erika Brittain, who did such a good job that she is going to leave the FDA next week, I wanted to thank her for helping us out with all this stuff.

Finally, I wanted to thank Leo Chan for putting together all the AV stuff and showing all the movies and everything that came out so well.

[Applause.]

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DR. LEGGETT: Have we begun to answer your questions?

DR. COX: I think we got a lot of very helpful advice today and I join John in thanking folks and also thanking the committee for all their discussions and helpful advice today.

DR. LEGGETT: Thank you. I think we will adjourn.

[Whereupon, at 3:50 p.m., the proceedings were adjourned.]

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