ANTI-INFECTIVE DRUGS ADVISORY COMMITTEE MEETING

November 18, 2008

BARTH RELLER: Good morning. I'd like to welcome you to today's convening of the Anti-Infective Advisory Committee of the FDA. I'm Barth Reller from Duke University in the Division of Infectious Diseases and International Health and Director of Medical Microbiology.

As a former member and chair of this committee, I've been asked to serve in an acting capacity for chairing today's session, tomorrow and Thursday.

I should like to begin with several remarks about how the process will work today, tomorrow and Thursday morning. For topics such as those being discussed at today's meeting there are often a variety of opinions some of which are quite strongly held.

Our goal is that today's meeting will be fair and an open form for discussion of these issues and that individuals can express their views without interruption. Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the Chair. To that end for those who are not familiar with the microphones, the upper right hand button with the speaker sign, when that is pressed the

red light comes on then we're ready to hear your contribution. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the government -- and the Sunshine Act, we ask that he Advisory Committee Members take care that their conversations about the topics at hand take place in an open forum -- in the open forum of the meeting.

We are aware that members of the media are anxious to speak with the FDA about these proceedings. However, FDA will refrain from discussing the details of the meeting with the media until its conclusion.

Along those lines there has been a change in the press handout having to do with the contact person for the FDA Office of Public Affairs. The contact person will be Karen Ripley (sic). Could you please stand up, Karen. Karen Riley. Thank you.

Also, the committee is reminded to please refrain from discussing the meeting topic during breaks or lunch such that all discussion of the topics at hand take place in the open forum of this meeting. Thank you.

We'll next hear from Dr. Janie Kim, who will read the conflict of interest statement. Dr. Kim.

JANIE KIM: Thank you, Dr. Reller.

The Food and Drug Administration is convening today's meeting of the Anti-Infective Drugs Advisory Committee of the Center for Drug Evaluation and Research under the authority of the Federal Advisory Committee act of 1972.

With the exception of the industry representative, all members and temporary voting members of the employees from other agencies and are subject to the federal conflict of interest laws and regulations.

The following information on the status of this committees compliance with federal ethics and conflict of interest laws covered by, but not limited, to those found at 18 U.S.C. Section 208 and Section 712 of the Federal Food and Cosmetic Act are being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary voting members of this committee are in compliance with federal ethics and conflict of interest laws under 18 U.S.C. Section 208(b)(3), Congress has authorized FDA to grant waivers to special government employees who have potential financial conflicts when it is determined that the agency's need for a particular individual's services outweighs his or her potential

conflict of interest.

Under section 208(b)(1) Congress has authorized FDA to grant waivers to special regular government employees who have potential financial conflicts when it is determined that the financial interest is not so substantial as to be likely to effect the integrity of the individual's service to the government.

Under section 712 of the FD and C Act, Congress has authorized FDA to grant waivers to special and regular government employees with potential financial conflicts, when necessary, to afford the committee essential expertise. Related to the discussions of today's meetings, member and temporary voting members of this committee who are special and regular government employees have been screened for potential financial conflicts of interest of their own as well as those imputed to them including those of their spouses or minor children and for purposes of 18 U.S.C. Section 208, their employers.

These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents, royalties and primary employment. For today's agenda the committee will discuss and make recommendations regarding justification of a

non-inferiority margin for complicated skin and skin structure infections. This is a particular matter involving specific parties. Based on the agenda for today's meeting, and all financial interest reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in conjunction with this meeting. With regard to FDA's speaker -- guest speaker, the agency has determined that the information to be provided by these speakers is essential.

The following interests are being made public to allow the audience to objectively evaluate any presentation and/or comments made by the speaker. Dr. Spellberg has acknowledged that he received research grants from Astellas Pharma, Merck, Novartis and Pfizer. He also recieved consulting fees from Basilea Pharmaceutica, Merck and speaker fees from Astellas Pharma. Also Dr. Spellberg was a scientific adviser at Merck.

With respect to FDA's invited industry representative, we would like to disclose that Dr. John Rex is participating in this meeting as a non-voting industry representative acting on behalf of regulated industry. Dr. Rex's role at this meeting is to represent the industry in

general and not any particular company. Dr. Rex is employed by AstraZeneca.

We would like to remind members and temporary voting members of the committee that if the discussions involve any other products or firms not already on the agenda for which a FDA participant has a personal or imputed financial interest the participants need to exclude themselves from such involvement and their exclusions will be noted for the record. FDA encourages all other participants to advise the committee of any financial relationships that they may have with any firm at issue.

Thank you.

BARTH RELLER: Having heard from Dr. Kim, designated federal official for this meeting, I next would like to have the committee members introduce themselves briefly with their affiliation. We'll begin on my left with Dr. Rex.

JOHN REX: Thank you, Dr. Reller. My name is John Rex. I'm a physician and board certified internist in internal medicine and infectious diseases, formerly Professor of Medicine at the University of Texas Medical School at Houston. I'm currently vice president for Clinical Infection at

AstraZeneca Pharmaceuticals. As Dr. Kim has noted my role on the committee today is that of a non-voting rep for the industry. In this role I represent regulated industry as a whole not my employer.

In addition, and potentially relevant to these conversations, I'm also the vice chair of the area committee on microbiology for the Clinical Laboratory and Standards Institute also known as CLSI or NCCLS, an international consensus organization that develops methods for testing and interpretations of microbiology results. I will also comment from that prospective when and if issues of microbiology become relevant during your discussions. Thank you.

PETER KATONA: Good morning. I'm Peter Katona. I'm an infectious disease physician from UCLA.

KEMPER ALSTON: My name is Kemper Alston. I'm an infectious disease specialist at the University of Vermont in Burlington and Fletcher Allen Health Care.

MATTHEW GOETZ: I'm Matthew Goetz. I'm chief of infectious diseases at the VA hospital in Los Angeles and professor of medicine at UCLA, infectious diseases and internal medicine trained.

THOMAS FLEMING: Thomas Fleming, Professor

of Biostatistics at the University of Washington.

JIM LEGGETT: Jim Leggett, Infectious Diseases, Providence Portland Medical Center in Oregon Health and Sciences University.

JACK BENNETT: I'm Jack Bennett from the National Institutes of Health.

TIMOTHY LESAR: Timothy Lesar, Director of Pharmacy, Albany Medical Center in Albany, New York.

LEWIS NELSON: Lewis Nelson. I'm a emergency physician and medical toxicologist at New York University.

ED SEPTIMUS: Ed Septimus, infectious disease physician, currently medical director of infection prevention at HCA Health Care System.

PHILLIP MIRKES: Philip Mirkes, developmental toxicologist from the Texas A&M University.

EMIL PAGANINI: Emil Paganini. I'm a retired head, section of ICU Nephrology Department of Nephrology at the Cleveland clinic and now a senior medical consultant for Critical Care Nephrology Consulting in Cleveland.

MARY ALICE SMITH: I'm Mary Alice Smith. I'm from the University of Georgia. I'm a professor in developmental and reproductive toxicology in the

Environmental Health Science Department.

MIKE SHELBY: I'm Mike Shelby. I work at the National Institute Environmental Health Sciences and Research Triangle Park, North Carolina. I'm the director of the Center for Evaluation and Risks to Human Reproduction.

JANICE POHLMAN: Good morning. My name is Janice Pohlman. I'm an acting medical team leader in the division of the Anti-Infective and Ophthalmology products with FDA.

THAMBAN VALAPPIL: I'm Thamban Valappil, Statistician, FDA.

SUMATI NAMBIAR: Good morning. I'm Sumati Nambiar, Deputy Director for Safety, Division of Anti-Infectives and Ophthalmology products.

KATIE LAESSIG: Katie Laessig, Deputy Director, Division of Anti-Infective and Ophthalmology products.

ED COX: Good morning. Ed Cox, Director of the Office Anti-microbial Products, CDER, FDA.

JANET CRAGAN: I'm Janet Cragan from the Birth Defects Branch at the CDC.

HENRY BLACK: I'm Henry Black from New York University from the Center for Cardiovascular Disease

Prevention.

JEANINE THOMAS: I'm Jeanine Thomas. I'm the patient representative and the founder of MRSA Survivor's Network and the national spokesperson for MRSA.

JIM STECKELBERG: Good morning. Excuse me. Jim Steckelberg, Division of Infectious Diseases at the Mayo Clinic.

ALAN CROSS: Alan Cross, Infectious Diseases, University of Maryland at Baltimore.

JOAN HILTON: Joan Hilton, Professor of Biostatistics, UC San Francisco.

ARTHUR LEVIN: Arthur Levin, Center for Medical Consumers and the consumer representative. infectious disease physician and Chief of Infectious Diseases at Robert Woods Johnson Medical School in New Jersey. I also direct the microbiology laboratory at our university hospital.

DEAN FOLLMANN: Dean Follmann, Head of Biostatistics at the National Institute of Allergy and Infectious Diseases.

KATHLEEN GUTIERREZ: I'm Kathleen Gutierrez, I'm -- pediatric infectious diseases at Stanford University,

Lucille Packard Children's Hospital.

CAROL KAUFFMAN: Carol Kauffmann, I'm Chief of Infectious Diseases at the Ann Harbor VA and Professor of Medicine at the University of Michigan.

BERNHARD WIEDERMANN: I'm Bud Wiedermann, Pediatric Infectious Diseases at Children's National Medical Center and George Washington University in Washington, DC.

JANIE KIM: Janie Kim, designated federal officer, FDA.

BARTH RELLER: Thank you all. We have tremendous expertise around this table and we look forward to your contributions. The next speaker, with a welcome and opening remarks, will be Dr. Katherine Laessig. Dr. Laessig.

DR. LAESSIG: Thank you. Good morning and welcome to this marathon meeting of the Anti-infective Drugs Advisory Committee. When running a marathon it's often helpful to break it down into smaller parts to make it less daunting. We can do that by considering our objectives for this two and a half day meeting.

Today, we are interested in establishing the treatment effect, sometimes known as M1, of antibacterial rugs

for skin infections. We're also interested in deriving a non-inferiority margin, sometimes called M2, based on clinical judgment of an acceptable loss of efficacy of the treatment effect.

We would also like to discuss trial design elements for skin and skin structure infections. Then starting tomorrow morning, we would like the committee to discuss and make some conclusions regarding the NDA for telavancin 22110.

Tomorrow afternoon, we would like the committee to discuss and reach conclusions regarding the NDA for oritavancin 22153 and finally on Thursday morning the NDA for iclaprim 22269. So what are complicated and uncomplicated skin and skin structure infections?

Well as described in the draft guidance for industry, cSSSI includes infected ulcers, burns, major abscesses and infections of deeper soft tissues. While uncomplicated skin infections refers to simple abscesses and impetiginous lesions, furuncles and cellulitis. More information can be found on the web at the address that is shown.

Some brief epidemiology of these infections. The majority is caused by Gram-positive organisms including staphylococcus aureus both methicillin susceptible and resistant

strains, streptococcus pyogenes and strep agalactiae. However, some complicated infections are associated with gram-negative rods and anaerobes. Certainly, I think everyone is well aware of the importance of community associated MRSA and skin infections. Recent data by Moran et al. in the New England Journal in 2006, demonstrated that MRSA was isolated from 59% with a range of 15 to 74% of adults presenting to ER's in 11 U.S. cities. While the active bacterial course surveillance as reported by the Klevens in JAMA of 2007 showed that 85% of invasive MRSA infections were healthcare associated and 14 were community associated.

So now I'm going to lighten things up by talking about the regulatory framework for your discussions. In 1962 the Food and Drug Cosmetic Act established the effectiveness requirement for substantial evidence which was described as, "Evidence consisting of adequate and well-controlled investigations including clinical investigations by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved on the basis of which it could be fairly responsibly concluded, by such experts, that the drug will have the effects it purports, etcetera, etcetera." So important language is adequate and well-controlled which is a

recurring theme.

As further described in the Code of Federal Regulations 21 CFR 314.126, it describes adequate and well-controlled studies. The purpose of conducting clinical investigations is to distinguish the effect of the drug from other influences such as spontaneous change in the course of the disease, placebo effect or biased observation. And the study uses a design that permits a final comparison with a control to provide a quantitative assessment of drug effect.

So why is this relevant for non-inferiority studies? Well the issue is that many of them don't include a concurrent placebo controlled and use only an active control. So in order to make conclusions about the studies, i.e. if the studies are informative, you need to know what the treatment effect is compared to placebo and generally you are relying on some type of historical information. Because without that you don't know whether you are having a scenario such as that shown at Figure 1 where you have a relatively large treatment effect compared to a placebo or on Figure 2 where you may not have much of a treatment effect compared to a placebo. It is also important to know what the treatment effect is in order to

define your non-inferiority margin. Because if you don't have that information you can't make a decision about what's reasonable to give up.

So back to the regulatory framework. Another important concept is when is it appropriate to rely on a single study. Well in the Food and Drug Modernization Act of 1997 investigation and confirmatory evidence may constitute substantial evidence. This is further discussed in the guidance for industry on clinical effectiveness and it's generally in cases where there's a single multi-center trial of excellent design with highly reliably and statistically strong evidence of an important clinical benefit, for example, survival; and there's pertinent information available which could include studies of other doses, regiments, dosage forms, other stages of disease, other populations or different end points.

So now to the overview of the agenda and the issues. Today we will hear presentations to review the evidence of the treatment of effective antibacterial drugs for skin infections and some non-inferiority margin justifications, by the agency, the three applicants and the Infectious Diseases Society of America. And I would like to thank the three companies and IDSA for their willingness to help us out in

today's agenda.

So the issues for your discussion are the susceptibility of the non-inferiority trials, appropriate margins and end points, timing of assessments and infection types for inclusion in new trials. So then starting tomorrow it's on to the NDA's. The first is telavancin. This application included two Phase 3 studies that compared telavancin to vancomycin. The issues for the committee's discussion are of the evidence of safety and effectiveness, the implications of the animal reprotox data for a use of the drug for pregnant women and women of child bearing potential and the need for any risk management.

Tomorrow afternoon will be oritavancin which will also included two studies. The first was a fixed dose of oritavancin compared to vancomycin and the second used two weight-base dosing regiments compared to vancomycin. The issues are the evidence of safety and effectiveness, considering the primary end point and confidence intervals, the outcomes in patients with MRSA and the weight-base dosing regiment that was used in study ARRD.

Thursday morning, we move to iclaprim which had two Phase 3 step studies, ASSIST-1 and -2, comparing iclaprim to

linezolid. And the issues are again evidence of safety and effectiveness, whether the committees sees any possible limitations of the use concerning the comparative outcomes of iclaprim and linezolid and whether there are clinicals where situations where iclaprim might be used.

I'd like to acknowledge the many people that were involved in pulling this advisory committee together, specifically those who worked on the identifying the evidence of the historical treatment effects, spent many hours in the library and then wrote background document. And also the review teams with the three NDA's, the advisory consultant staff without whom we couldn't pull this off.

So it's time to get started and I invite Dr. Valappil up to the podium who will walk us through

THAMBAN VALAPPIL: Thank you, Dr. Laessig.

Good morning, I'm Thamban Valappil. I'll be talking about the non-inferiority design issues and some considerations for the definition of non-inferiority margin for complicated skin and skin structure infections. The outlay of my presentation is as follows: Objectives in a non-inferiority trial, critical elements, statistical uncertainties, limitations of meta-analysis, discounting and preservation. And I will

conclude the presentation with the steps involved in the non-inferiority margin determination for complicated skin and skin structure infections.

What are the objectives in a non-inferiority trial? Non-inferiority trials are designed to determine whether the effect of a new treatment is not unacceptably worse compared to an active controlled treatment, based on a pre specified non-inferiority margin. And, ensure that the control effect related to placebo is consistent under the conditions of the trial.

Now what is the difference between a superiority and non-inferiority trial design? Superiority trials provide direct evidence of treatment effect. Then the objective is to demonstrate that the new drug is statistically superior to placebo or to an active control. Superiority trials are always preferred if possible. Whereas, non-inferiority trials provide indirect evidence of treatment effect.

Therein, any new treatment must be compared to established active control that has demonstrated treatment effect based on data external to the trial. Data external to the trial in the sense that non-inferiority trial does not include a placebo arm and hence the comparison of the new

treatment to an active control is based on the strong assumption that the controlled drug is significantly superior to a placebo based on historical studies with a large treatment effect.

Also the interpretation of the results in a non-inferiority trial can be misleading due to potential lack of assay sensitivity and/or constancy assumptions. Now what is a primary hypothesis in a non-inferiority trial? In a non-inferiority trial, the null hypothesis is that the degree of inferiority of the new drug, denoted by T to the control C, is greater than or equal to the margin or predefined margin M. As you can see here the null hypothesis is stated as the test drug is inferior to the control and alternate hypothesis is the test drug is not inferior to the control.

Therefore, non-inferiority will be concluded if the lower bound of the two-sided 95% confidence interval for the difference between test drug and the control drug is less than the predefined margin M.

Now let us look at the components of a non-inferiority margin. There are two components, M1 and M2. from a historical placebo controlled studies and it is a statistical margin. Whereas M2 is a clinically acceptable loss

of efficacy for the new drug compared to the active control with respect to the primary end point of interest. M2 is strictly less than M1.

According to the ICH-E10, the non-inferiority trial design is appropriate and reliable only when the historical estimate of the drug effect size can be supported by in reference to the results of previous studies of the control drug. A non-inferiority margin is defined as the largest difference that can be judged as being clinically acceptable and should be smaller than the difference observed in superiority trials of the active comparator. The margin chosen for a non-inferiority trial cannot be greater than the smallest effect size that the active control drug would reliably expected to have compared with placebo in the setting of the planned trial.

The question now is, when is proper to consider a non-inferiority trial design? So in the coming slide I have two different scenarios as you can see here, there are four placebo-controlled historical studies with the varying point estimates and the corresponding 95 percent conference intervals. The meta-analysis is shown here on the bottom to look at the collective evidence. As you can see here the lower limit points to a 20 percent treatment effect as highlighted here on this

slide. Now this is probably a good candidate for deriving a non-inferiority margin to design future non-inferiority trials. Whereas in this scenario as you can see the control effect is very small probably due to the high spontaneous resolution rate for placebo and this is -- in this situation we may not be able to come up with a non-inferiority margin for designing future trials.

Now what are the critical elements for non-inferiority trials? Historical evidence of sensitivity to drug effects assay sensitivity and constancy of the active control effect are the three important elements. Historical evidence of sensitivity to drug effect exists if an active control drug has reliably demonstrated a superior treatment effect compared to a placebo or some other related drug, based on an appropriately designed and well conducted historical studies using a particular end point of interest. Whereas assay sensitivity refers to the ability of the non-inferiority trial to distinguish an effective treatment from a less effective or ineffective treatment. Evaluating whether a trial will have assay sensitivity is based upon historical evidence of sensitivity to drug effect, similarity of the non-inferiority trial to the historical studies and quality and conduct of the

non-inferiority trial.

Constancy of the active control treatment effect refers to the similarity of the current non-inferiority trial to the historical studies. The conclusion that HESDE can be used for future non-inferiority trials is possible only if the non-inferiority trial is sufficiently similar to the historical studies with respect to all important study design features that metric chosen to represent the treatment effect is an important factor to consider as well. For example, risk difference, relative risk, odds ratio or hazard rate can all have different interpretations when it comes to the constancy of the control effects.

Now what are the -- what are some of the statistical uncertainties in non-inferiority trials? For example, lack of reliability, uncertainty in magnitude and lack of precision of the active control treatment effect can be a serious problem. Validity of constancy assumption is another issue. The other question is can we assume that the active control treatment effect in the non-inferiority trial and historical studies is similar.

Poor trial design can introduce bias and has the potential to erroneously conclude non-inferiority.

Noncompliance, misclassification of outcomes and informative missing values are problematic issues as well. Simulations studies have shown that misclassification of outcomes can inflate the overall type-1 error rate in a non-inferiority trial, in some cases dramatically. Confounding factors such as the use of concomitant medications or adjunctive therapies can potentially bias the efficacy results.

We have used meta-analysis to obtain collective evidence of treatment effect from historical studies and there are limitations in the historical studies, as we are going to discuss that in Dr. Nambiar's presentation and she's going to go through the historical studies in great detail. Some of the limitations include the tendency to overestimate the treatment effect due to publication bias, pulling effect size from studies in which the historical estimates may not be stable.

For example, the observation studies or case studies. Heterogeneity in treatment effect due to differences in disease characteristics, endpoints and design features can have issues with the control effect. Analysis including small and large studies or limited data can also effect the generalizability of the results.

Now let me discuss the M1 and M2. The historical evidence

-- or the historical active control treatment effect compared to placebo is derived using a two-sided 95 percent conference interval for the treatment difference between the active control and placebo.

Therefore it is important to discount also for all the potential uncertainties based on the issues I discussed earlier. The non-inferiority margin M2 is derived based on preserving a fraction of the discounted M1 using clinical judgment. Substantial preservation of the treatment effect ensures that the new drug is more effective than placebo.

Now let me discuss about the discounting and the preservation concept. Discounting is the reduction in magnitude of the active control treatment effect determined from the HESDE to account for the variability and statistical uncertainties. Whereas preservation is a proportion of the control effect preserved based on clinical judgement. Higher rate of preservation is warranted when treatment failures result in irreversible outcomes such as mortality. For example, if you have a control effect of let us say 40 percent based on mortality, now we cannot preserve only 50 percent of that effect in designing future trials. This would make the new drug be 20 percent inferior to the control for mortality. So

in that scenario we might need to preserve more than 50 percent.

Now this is a slide to illustrate the discounting preservation concept. As you can see, there are four historical studies, placebo controlled studies, the point estimates are marked in different colors to indicate the variability across the studies. So here, just like in the previous slide, the point estimate of the treatment difference between the control and placebo and the corresponding 95 percent confidence intervals are shown here. The collective evidence, based on the meta-analysis, indicates a 20 percent effect -- treatment effect. However, if we discount for 50 percent of that effect, for the uncertainties, that would give us an M1 of ten percent. And if we preserve 50 percent of that effect that will give us a margin of five percent. Again, this a hypothetical scenario. That's the reason I marked it in gray color. Again,the discounting is an arbitrary decision, that is why the reason why I have marked it in gray colors.

Now let us assume that we have conducted a non-inferiority trial. Now how do we interpret the results of the non-inferiority trial? The treatment difference between the test drug and the corresponding 95 percent conference intervals are shown here for five different scenarios. As you can see in

the first two scenarios, if you look at the allowable limit of the 95 percent conference interval around the treatment difference, they rule out the non-inferiority margin which is marked on the left side, with the yellow dotted line.

However, the second scenario shows a better treatment effect. As you can see from the point estimate it is about zero. However there's a large variability around that estimate. The third scenario, as you can see the lower limit falls below the non-inferiority margin and hence fails to demonstrate non-inferiority.

In this scenario, fourth scenario, as you can see the lower limit, as well as the point estimate of the difference, both are well above zero, indicating superiority. Also it is simultaneously demonstrating non-inferiority as well. The fifth scenario is particularly interesting. As you can see the lower limit is above the margin, shows -- demonstrates non-inferiority. However the upper limit fails to cross zero, showing statistical inferiority of the test drug to the control. Now the probability of that upper limit crossing zero is only 2.5 percent or less.

Now having discussed all the issues with the non-inferiority trial designs, let me briefly go over the steps

involved in the non-inferiority margin determination for complicated skin and skin structure infections. Estimate complicated and uncomplicated skin and skin structure infections, assess constancy of the treatment effect considering disease, patient population and micro-organisms. M1 is estimated based on accounting for statistical uncertainties and variability. And finally, determine the margin based on clinical judgment of an acceptable loss of efficacy. With that I conclude my presentation. And I would like to invite Dr. Nambiar to continue with the presentation.

Thank you.

DR. NUMBIAR: Thank you, Dr. Valappil and good morning everybody. In my presentation today I will provide some details about the agency's approach to determining non-inferiority margin in complicated skin and skin structure infections.

Outline of my presentation is as follows. I'll briefly discuss some regulatory background and touch upon the highlights of contemporary cSSSI trials. I'll review historical studies that we used to estimate the treatment

effect of antibacterials in skin and skin structure infections. I'll discuss the derivation of treatment effect and discuss uncertainties in the estimate of the treatment effect.

Most recent registrational trials for the indications of complicated and uncomplicated skin and skin structure infections have been non-inferiority trials. The NI margin used has varied from 10 to 15 percent. There have been several discussions on the use of active control non-inferiority trials as basis for approval of antimicrobial agents. In October of 2007 a draft guidance in this regard was published. Currently sponsors are being asked to provide evidence to justify the proposed non-inferiority margin for all indications.

Several antibacterial agents are approved for the treatment of complicated skin and skin structure infections. I've just cited a few examples here, such as quinupristin/dalfopristin, linezolid, ertapenem, daptomycin, tigecycline, meropenem, moxifloxacin. There are several older

anti-bacterial agents which are approved for skin and skin structure infections indication and not being differentiated as uncomplicated or complicated. And I've listed a few examples here.

As Dr. Laessig had mentioned, patients who are enrolled in current cSSSI trials meet the definition of cSSSI as outlined in our draft guidance. This includes infections that involve deep soft tissue or require significant surgical intervention, such as infected ulcers, burns or necrotizing fasciitis, secondly infected dermatoses and infections involving prosthetic materials are excluded from such trials.

Active comparators used in some of the recent trials include vancomycin, linezolid, semi-synthetic penicillins and others that I've listed here. Some studies or trials have allowed for concomitant aztreonam or metronidazole and some trials have allowed for oral switch after a period of parenteral therapy if certain clinical criteria suggestive of improvement are met.

The surgical interventions and local

adjunctive therapies that have been allowed have varied across studies. Some trials have differentiated bedside surgical procedures, was from those that are planned and performed in the operating room. The treatment duration in most trials has varied from 7 to 14 days.

The primary end point is clinical response of cure or failure which is based on resolution or improvement or signs and symptoms and the need for further anti-bacterial therapy as assessed by the investigator. The test of cure assessment has generally occurred about 7 to 14 days after the end of therapy.

This is our approach to estimation of NI margin and has been briefly discussed by Dr. Valappil. We estimated the anti-bacterial treatment effect for both complicated and uncomplicated skin and skin structure infections. We assessed constancy of the treatment effect, taking into consideration factors such as disease definition, patient populations, the causative micro-organisms, end points assessed and the timing of their assessment.

We estimated M1 accounting for uncertainties and we determined that M2 or the NI the NI margin based on clinical judgment, preserving a fraction of M1. Our Methodology in reviewing and identifying studies was as follows. We conducted a fairly comprehensive literature search to identify the historical studies.

However, for purposes of quantifying the treatment effect we used data primarily from comparative studies in order to avoid cross study comparisons between treatment arm and control arm. We used studies were the end point assessed was relatively well defined and was not limited to mortality alone. We also reviewed studies where the timing of end point assessment again was fairly well specified. These are historical studies so they're not really perfect. We used studies where the specifically excluded studies which only provided microbiological end points. Natural history studies and single arm studies were used as supportive data.

So these are the types of studies we reviewed to derive the antibacterial treatment effect. As I mentioned we reviewed natural history studies. We looked for placebo controlled studies in complicated skin and skin structure infections, but

unable to identify any.

However, for the indication of uncomplicated skin and skin structure infections at least a few placebo controlled studies are available. We were primarily limited to indications impetigo and superficial abscesses. We reviewed studies were patients treated with antibacterials were compared to standard of care which did not include antimicrobial therapy. And these were primarily limited to patients who had either erysipelas or a series of patients who had hand infections. In addition, we reviewed case series of penicillin or sulfonamide treated patients, there was no comparator or control arm in these studies.

So I'll briefly touch upon three natural history studies just to give you a perspective or understanding of what happedned prior to the availability of anti-bacterials. This publication by Meleney from 1924, this provides one of the earliest descriptions of untreated streptococcal gangrene. Twenty patients were described seven of whom were bacteremic. Some patients did recover with wound care alone while the most severe ones progressed to systematic symptoms and often death. Treatment consisted only of wound care and included incision and

drainage, excision of gangrenous skin, use of hot water soaks and Dakin's Solution. Important, in terms of the outcome was that 15 of these patients did recover and the mortality was only 20 percent which we'll see much less than what I'm going to discuss in my next two slides. But I think the point we want to make here is that even though mortality was not very high, recovery occurred over a very prolonged period of time. Several patients required skin grafting and the average time to grating was 50 days. Some patients also had to undergo amputation of the affected limb. This publication by Keefer in 1937 describes 246 patients with hemolytic streptococcal bacteremia. And the overall mortality here was much higher than we saw in the previous study with the overall mortality at 72 percent.

About 25 percent of patients in this series had cellulitis or erysipelas as the source of bacteremia and 80 percent of these patients died. Skinner and Keefer described 122 cases of staph aureus bacteremia seen at Boston City Hospital only 22 patients recovered. In almost 50 percent of these patients the portal of entry was the skin and the type of infections included boils, carbuncles and infected wounds. Eighty-four percent of patients who received only general care succumbed while about 79 percent of patients who received general care, plus sulfonamides died.

All four patients treated with anti-toxin died as well. detail was studies where patients, treated with anti-bacterials, were compared to those who received standard of care which did not include the use of antimicrobials. Before I move on discussing the studies, I just wanted to point out that erysipelas, though not always a severe disease, can be associated with mortality in the mostly severe cases, especially at the extremes of age. And this figure that I got from a publication by Keefer in 1938 -- the arrow in red points to the mortality and as you can see in the first decade of life and after the seventh decade of life mortality is very high and it's above 60 percent. An important point also is that in the other decades of life there was still mortality and this would be in the range of about 15 percent, an average mortality before the availability of antibacterials. And this line here really just represents the incidents by age.

Snodgrass and Anderson conducted two studies in patients with erysipelas and I'll describe both of them in some detail. This is the first of the two studies which was conducted from -- sorry -- February of 1936 to May of 1936 at one hospital in Scotland. Three hundred and twelve cases were included in this series and this was done to assess the

treatment benefit with prontosil, a simply antibacterial that was later shown to be a pro drug of sulphanilamide. The first 161 cases in the series were allocated to three groups in the order of admission, to be treated with either UV light alone, prontosil alone or UV light plus prontosil.

The second 151 cases were also allocated to three groups. The first two groups were the same as that in the first series. The third group was treated with scarlet fever antitoxin. The authors note in this publication, that the duration of disease before admission to the hospital, age of the patient, severity of the infection and associated diseases were similar in the groups. The actual numbers or comparisons between the two groups are not provided in the publication. They also note that all groups were treated unter similar conditions in terms of wards where they were treated and the the nursing staff. Treatments was given during the acute stage only and each case was reviewed daily. Now in this table we have provided the outcomes at 48 hours.

I just want to make a point that even though we say the outcomes are at 48 hours, it was not a precise estimate exactly at 48 hours, the assessment conducted on day two, after 48 hours of treatment. The three end points that the authors had

evaluated were cessation of the spread of lesions, resolution of pyrexia, and resolution of toxemia.

The definition of toxemia used by the authors was fairly subjective and so for our purposes of this exercise we have not used that particular end point but I would like to note that there was a treatment effect even for that particular end point. So for cessation of spread of lesion as assessed after 48 hours of treatment in the prontosil group 98 percent of patients had cessation of spread of lesion compared to 76.5 in the UV light group for a treatment difference of 21.5 and in parenthesis are the 95 percent confidence interval. I'm sorry, I think the numbers in red font are not in your handout. So because patients who died were excluded from this case series by the authors, we did a sensitivity analysis where all patients who died were considered failure and these numbers in red indicate results from those scientific analysis. And there is not much of a difference so for purposes of our discussion this morning we are just going to use the numbers in black font. Similarly, for the end point of resolution of pyrexia after 48 hours of treatment patients in the prontosil group did much better, 76 percent were afebrile compared to 48 percent in the UV light group, for a treatment difference of 27.8 and the confidence in parenthesis. Again the

numbers in the red font are results from our sensitivity analysis. This is a graphic of representation of the same data, but we have provided the results beyond 48 hours. Again interestingly, the greatest treatment difference is in the first two days and by day five really both the graphs meet. I would like to point out that by day two, in the prontisil group we are down to one or two patients who still had -- in whom the lesions had not ceased to spread.

This is a second study again by the same two authors done at the same institution. The main objectives of this study, because they had already seen the benefits of prontosil and by this time it was known that prontosil was in fact a pro-drug of sulfanilamide this study was really done to study the treatment benefit of sulfanilamide and erysipelas. They also wanted to study the effects of a larger and more prolonged dose of sulfanilamide and they also used varying dosage of sulfanilamide within the first 12 hours and wanted to see if that made any difference on the treatment outcome. Of the 270 cases, 135 were assigned to each of the two treatment groups. The doses of sulfanilamide used were one, two or three grams given every four hours till they were afebrile followed by 0.75 grams three times a day till patients who were discharged.

Again, as in the previous publication the authors state that the two treatment groups was similar in terms of patient characteristics and were treated under similar conditions.

Again, as we have seen in the previous study the outcome at 48 hours rarely affect outcomes after 48 hours of treatment as assessed on day two. Patients in sulfanilamide arm did much better in terms of cessation of spread of lesion. There was only one patient whose lesion had not yet stopped spreading compared to UV light group where it was 73 percent. It gives you treatment difference of 26.3 and the 95 percent CI. Again, these are the results of a sensitivity analysis we did wherein the six fatal cases and the 12 failed UV cases who were later treated with sulfanilamide were considered failures and these are the results of the sensitivity analysis. And as you can see the lower bound goes up to 17.5 to 20.2 and here from 15.1 to 17.5. Again, this is a graphical representation of the data with the greatest treatment effect being seen in the first couple of days and by day three there is not much of a

We then did a random effects meta-analysis using results from these two studies with the two end points of cessation of spread of lesion and resolution of pyrexia. These are the results for the end point of cessation of spread of

lesion. And as you can see here the treatment effect is -- point estimate was 24 percent and these are the 95 percent confidence intervals from 18.2 point to 30, clearly favoring treatment with sulfanilamide or prontisil compared to UV light. The resolution of fever at 48 hours, again the results were very similar. The point estimate was 27.8 with a 95 percent confidence intervals 18.92 to 36.8 clearly favoring sulfanilamide or prontisil.

In the 1920's and 1930's there are several publications available on various treatment modalities that were used for erysipelas. We reviewed several of these historical studies especially the ones that compared UV light to other topical therapies because in both of the Snodgrass publications sulfur drugs were compared to UV light and not truly placebo.

In most of these studies patients treated with UV light have better outcomes compared to those treated with various local therapies, including glycerin iodine magnesium sulfate. And in the UV light treated cases there was both a reduction in mortality as well as improvement of time to resolution of signs -- of local signs of erysipelas -- and fever was shorter in UV light treated patients. We were unable to UV light relative to these other local modalities of treatment as

the studies did not provide results on proportion of patients who had complete resolution of signs and symptoms after fixed time point. Most of these studies provided results in terms of average time to resolution or mortality or average time to hospitalization.

So to summarize the treatment effect of inpatients with erysipelas. Based on the two meta-analysis that I have shown you, the treatment effect for sulfonamides over UV light, for the two clinical end points assessed after 48 hours of treatment is as follows. For cessation of spread of lesion the point estimate for the treatment difference is 24.1. And the variability around that estimate is 18.2 to 30. For the end point of resolution of fever the point estimate is 27.8 and the 95 percent confidence intervals around this estimate 18.9 to 36.8.

It does appear from the other historical settings that UV light had a beneficial effect compared to various local therapies. So we think that the treatment effect of sulfonamides over placebo is likely to be greater than the effect of sulfonamides over UV light.

This is the next publication that I will discuss in some detail. This is a series of 212 cases of acute

hand infections that were described by Florey in Lancet 1944. These are not war wounds, but they are acute infections of various types which were primarily confined to the hand. I have to admit there were a few patients here who had infections that to assess the benefit of topical penicillin because this occurred around -- the study was done around the time that penicillin was in short supply and parenteral penicillin was not a good option. Alternate cases were assigned to receive penicillin. All cases were treated with topical penicillin. Three patients in the penicillin arm -- three penicillin patients did receive oral sulfonamides. Controls received various local applications and in the most severe cases received oral the sulfonamides. The authors do acknowledge that these are not perfect controls, so they in fact call them contrasts rather than controls.

Surgical method used in both groups was similar and the same surgical team operated on both groups. Patients in the control arm were treat -- the local care provided to patients in the control arm included the use of paraffin, gauze and operation and later they were treated with topical eusol. In the penicillin group the wounds were treated with a calcium salt -- powder form if calcium salt of penicillin and later

packed with gauze soaked in penicillin paste. In both groups dressings were repeated daily for a minimum of five days. During the acute phase patients were followed every day. Thereafter it was about twice a week. And interestingly long term follow-up was provided all the way out to six months especially to access recovery of hand function. Group A streptococci and staphylococcus aureus were the most commonly identified organisms in the series.

This table summarizes the types of infections seen in this group in these 212 patients. Again, the numbers are small, but between the two arms they are fairly similar. Patients had paronychia, simple pulp infection, web-space infection, infection of the tendon sheath, abscesses and others such as septic lacerations and septic dermatitis.

Next in a series of graphs we've tried to present the treatment difference as best we could discern from this paper. Now this paper does not provide us results of proportions cured, they only gave us the average time to a certain end point which really depended on the type of infection. So for the paronychia the end point that the author assessed was drying of lesion. And it's very clear from the graph here that patients in the penicillin treated group did

much better than those in the control group. And another important part is the wide variability in the control group in terms of time to drying of the lesion.

For simple pulp infections more than one end point was looked at by the authors. They looked at disappearance of pus, they looked at drying of lesion, epithelization of the wound and full movement. Again, if you look at the point estimates for each of these end points it's very clear that patients treated with penicillins did much better than patients treated with control. We have to acknowledge that there's a wide variability around all of these estimates and the 95 percent confidence intervals do overlap. But again the confidence intervals or the variability in the see in the control group.

For Patients with web space infections, again the three end points were disappearance of pus, return of full movement and complete healing of the wound. Again, as in the previous graph point estimates clearly favor penicillin treated patients. There is a variability around the estimate and overlap in the confidence intervals. These are patients who had tendon sheath infections, again for the various endpoint. The message is the same that overall penicillin treated patients did

much better. We acknowledge the variability, but the numbers in each of these subgroups was fairly small. And these are patients with abscesses -- I'm sorry.

For drying of pus there is -- clearly the penicillin treated patients did well, but in terms of drying there is really no difference between the two groups. So if all of the end points that were presented in this paper and the ones that I discussed, we thought the end point of disappearance of pus most clearly represented antibacterial treatment effect. And so we look at this particular end point in some more detail. So for the four kinds of infections, pulp infections, web space infection, infection of the tendon sheath and abscesses, these are the mean time to resolution of -- mean time to disappearance of pus in the control arm in the penicillin treated arm. Again, it's very clear that across the board patients treated with penicillin did much better. Again we acknowledge there is variability in the point estimate primarily because of the small numbers. The numbers in parenthesis give you the number of patients in each of these -- patients with each of these infections in the two arms. So to summarize the treatment effect from this publication, overall it appears that penicillin treated patients had better clinical outcome. Pus had

disappeared over scanty with a week from surgery. In controls the range is very wide. It continued anywhere from three to 113 days. Mean healing time in penicillin treated patients was reduced. There was a great reduction in the number of dressings required and rapid return of mobility of the infected part. Interestingly, the authors also looked at the working time saved by penicillin. They only had adequate data from 35 penicillin treated cases and 35 controls with either pulp and tendon sheath infections and the working time saved here was 1,0000 days.

Moving on to the next type of historical studies that we reviewed, and I will not spend too much time here because these studies don't help us in terms of quantifying the treatment effect, but nevertheless provide supportive evidence. These are two small series of patients treated with sulfonamides in the publication by Long. All seven patients who had skin and skin structure -- of the seven cases with skin and skin structure infection six recovered. In Keefer's publication from 1938 only 33 percent of patients with hemolytic streptococcal bacteremia died in contrast to 70 to 80 percent before the availability of even sulfonamides. These are case series of patients treated with penicillin which could either be

Lyons described patients with several kinds of infections treated with penicillin but the number here only represent patients who had skin and skin structure infection and the overall cure rate was 86 percent.

Garrod described 171 cases of infected soft tissue wounds. Patients were treated with local penicillin and the failure rate was only 4 percent; 61 percent had complete union and another 35 percent had subtotal union which is healing by granulation tissue.

Meleney described 744 cases of surgical infection. These -- all of them are not patients with skin and soft tissue infection. They include a variety of surgical infections. Three hundred and forty of them had infections of the skin and skin structure the overall cure rate was 72 percent.

These were the types of skin and skin structure infections seen in the 744 cases describe by Meleney. Sorry. And as you can see here the cure rates really vary depending on the type of infection. Much higher cure rates in patients who had furuncles or cellulitis, lower cure rates in patients with infected wounds or ulcers.

These are two large series of patients treated with penicillin. I'm not going to spend too much time on these

because only small number of patients in both these series in fact had skin and soft tissue infection.

So then I'm moving on to uncomplicated skin and skin structure infections where we were able to identify a few placebo controlled studies. We classified them based on the type of -- the uncomplicated skin and skin structure infection. In patients with impetigo there are placebo controlled studies that accessed topical antibacterial therapies. Retapamulin was compared to placebo in a fairly recently conducted Phase 3 trial. We were able to identify two historical studies where mupirocin was compared to placebo. Then there were three -- we identified three placebo controlled studies where systemic antibacterials were compared to placebo in patients with other superficial skin infections. Some of them did have -- include patients with impetigo, especially the Burnett study. Eaglstein study was really patients with secondly infected dermatoses and a study from Bower was a whole variety of uncomplicated skin and skin structure infections. We also looked at two studies in patients with superficial abscesses where antibacterial therapy was compared to placebo in addition to incision and drainage.

This is a summary of treatment effect in patients with

impetigo. Retapamulin is a topical pleuromutilin that was approved in 2007 for the treatment of impetigo. A Phase 3 study was conducted where retapamulin was compared to placebo. The cure rate in the retapamulin treated patients was 85.6 compared to 52.1 in the placebo treated patients. The outcome was accessed on day seven after a five day course of treatment. Treatment difference of 33.5 in the 95 percent confidence intervals, 19.4 to 47.6. In the Gould study patients with provided the point estimates and the treatment difference in these two studies. Again because of the small numbers there's a wide variability in the estimate of the treatment effect. In the Eells study I'd just like to point out there were 27 percent of patients were unevaluable. So we reclassified them as failures and these numbers reflect that. Whereas in the publication you have numbers from the evaluable population.

We conducted a meta-analysis using three -- these three studies and acknowledging that both the Gould study and the Eells studies were not perfect trials. The point estimate for the treatment effect was 28.8, low bound of 18 and upper bound of 39.6 again favoring topical therapies. Now given the limitations of the Gould and the Eells study, the retapamulin study on its own, with 95 percent confidence intervals of 20.5

to 46.5, because it's a single study we also looked at the 99 percent confidence intervals and the lower bounds was 13.

So having reviewed all the historical studies, I would now like to summarize what is the antibacterial treatment effect we were able to discern in skin and skin structure infections. So using the studies were sulfonamides were compared to UV light in patients with erysipelas where the end points were assessed after 48 hours of treatment for cessation of spread of lesion, the point estimate for the treatment difference was 24.1, the 95 percent confidence intervals into around this estimate, 18.2 to 30. For resolution of fever the point estimate was 27.8, 95 percent confidence intervals 18.9 to 36.8. Studies that compared topical antibacterials to placebo and impetigo and both of these based on the meta-analysis that I've shown you, the end point assessed here was at the end of therapy about day seven to nine. And the end point was defined as resolution or improvement in signs and symptoms. Point estimate was 28.8, the 95 confidence intervals around this estimate were 18 to 39.6. In the single study that compared systemic erythromycin to placebo in patients with impetigo and other uncomplicated skin and skin structure infections -- Sorry, this is the Burnett study from 1962. The timing of assessment was not very clear in

the publication but the authors note that continual improvement did not occur, they were declared a failure. The study does mention that patients were assessed on about day three or four and every three to four days later so we are assuming that the treatment was estimated some point after day seven. The end point here was resolution or improvement in signs and symptoms. The point estimate was 61.9 and the 95 percent CI, 43.5 to 80.3. These results of the cephalexin was compared to placebo in addition to incision and drainage in patients with superficial skin abscesses, was the Rajendran study from 2007, the end point was accessed at the end of therapy seven days after incision and drainage. The end point was resolution of signs and symptoms. Antibacterials offered no benefit beyond what is achieved by incision and drainage alone.

Natural history studies -- in natural history studies bacteremia, some of who had skin was portal of entry was very high, in the range of 70 to 80 percent. And there was a significant reduction of mortalities since the introduction of antibacterials.

Do we think that the antibacterial treatment effect seen in this historical studies is applicable to contemporary cSSSI trials? We think in cSSSI, as currently defined, it is likely

that the treatment effect will at least be the same or greater than that seen in the studies of erysipelas or impetigo. We did note that the benefits of antibacterials was seen in several types of skin infections. They were really not limited only to patients with erysipelas or impetigo. And the kinds of infection we have seen in historical studies are not very different from the types of infections seen in patients who were enrolled in current cSSSI trials. Staph aureus and streptococcus pyogenes were the main organisms isolated in historical studies and are also the two most common organisms identified in present trials. So, we think you could certainly derive some treatment effect from the historical studies. Having said that are there any uncertainties in our estimated treatment effect and the answer would be, yes.

The first point I would like to make is in terms of end point. In the studies in erysipelas that I reviewed with you this morning, the treatment effect was assessed early on after 48 hours of treatment. However, it's important to note that the end point assessed in those trials was cessation of spread of lesion and not resolution of lesion. And also another important point is that in present trials patients who were not improving by 48 to 72 hours of therapy are classified as failures and are

switched to alternative therapies. So in fact, there is an assessment that happens somewhere in the 48 to 72 hour window.

In studies of impetigo treatment effect was assessed at the end of therapy about seven to nine days after the stop of therapy. And in patients with hand infections described by Florey, even at the end of week one there was a treatment difference between the penicillin treated patients and the controlled patients.

In terms of patient populations, needless to say patients in historical studies will not be identical to the patients who are enrolled in present trials. Patients in present trials tend to have more co-morbidities such as obesity, diabetes and renal impairment, all of which can affect the clinical outcome. On the other hand ancillary care including wound management is likely to be superior in present trials.

Another important point is that cSSSI is not a single clinical condition. It represents a spectrum of diseases. So you do see higher cure rates in patients with infections such as cellulitis and lower cure rates in those with wound infections or ulcers. We'd also like to point out that patients with superficial abscesses, antibacterials don't seem to provide any benefit beyond that achieved with incision and drainage.

However, the applicability of this information to deeper and larger abscesses as are enrolled in cSSSI trials is uncertain. underestimate in the onset and that would be yes, because treatment effect with present day antibacterials is likely to be higher than that seen with sulfonamides or topical penicillin in the historical studies. And as I mentioned earlier on in my presentation, treatment effects with sulfonamides over placebo is probably more than what was seen over UV light.

Could the treatment effect be an overestimate? The answer to that is yes as well. Because the treatment effect that we derived in studies of erysipelas was based on cessation of spread of lesion which is very easy to identify in patients with erysipelas and may not be directly applicable to all types of cSSSI. And with improved wound care and supportive care, the treatment effect due to bacterials, separate from that of wound care, is difficult to discern.

So in conclusion, in erysipelas there is a treatment benefit for the critical end points of cessation of spread of lesion and resolution of fever as assessed after 48 hours of treatment. In impetigo there is a treatment effect for the clinical end point of cure based on resolution or improvement in signs and symptoms at the end of therapy. In superficial skin

abscessed there appears to be no treatment effect with antibacterials beyond that achieved with incision and drainage alone.

Natural history studies and case series provide supportive evidence for the antibacterial treatment effect in cSSSI. As we go through the discussions and deliberations for today we would like you to consider the following three points.

Can we assume that the treatment effect for cSSSI is at least as large as that seen in studies of erysipelas or uncomplicated skin and skin structure infections? Can we conclude that the historical treatment effect of antibacterial drugs in cSSSI is quantifiable based on on historical data presented, given its limitations. And if in fact the treatment effect is quantifiable how much of it should be discounted and how much of it should be preserved?

So having gone through this exercise this morning, I think I would have convinced you that antibacterials actually work in patients with skin infections. And I leave you with this quote from a publication from Hosford in 1938 which clearly outlines the benefits of sulphanilamide beyond reduction and beyond the effect of reduction and mortality. Thank you.

BARTH RELLER: Are there any question for Dr. Nambiar or

Dr. Valappil related to their presentations? Yes, Dr. -- please.

DEAN FOLLMANN: Thanks. I just had a couple of questions of clarification on the impetigo studies. So these were done in a more modern era in the 1980's and so on. Were these randomized, double blind placebo -- they were placebo-controlled trials? A technical question, when you did the meta-analysis of those three studies of impetigo, did you use a random effects model, use a fixed effects model?

SUMATI NAMBIAR: Thamban, you can correct me if I'm wrong. For the two erysipelas studies we used a random effects

DEAN FOLLMANN: Did you check for heterogeneity of the treatment effect for the impetigo studies?

SUMATI NAMBIAR: Yeah, I think the impetigo studies we know going in that both -- the two studies were much smaller and one was in fact only a subgroup. So we just looked at the one large study and we did the 99 percent CI and the lower bound was I think, 13 percent.

DEAN FOLLMANN: And then finally, for the impetigo studies, was there a concomitant therapy or rescue therapy given that or was it a straight comparison of drug versus placebo?

SUMATI NAMBIAR: Concomitant --

DEAN FOLLMANN: Were there other therapies that were given to both groups to try and cure the infection or is it just placebo versus treatment?

SUMATI NAMBIAR: Not that I'm aware of. I think it's a straight comparison.

BARTH RELLER: Thank you for those questions, Dr. Follmann. Dr. Wiedermann.

BERNHARD WIEDERMANN: Thank you, Dr. Nambiar. These were also somewhat related technical questions. You didn't mention your literature search strategy, but it looked like it was only English language. Do you know or did you do any testing for publication bias?

SUMATI NAMBIAR: No, we didn't do any formal testing for publication bias. It's just -- reviewing the historical studies was quite challenging so --

BERNHARD WIEDERMANN: I bet.

SUMATI NAMBIAR: -- we used an old-fashioned approach which is when we found a cross reference then we would go find that cross reference. So that's how we sort of kept building up on our articles. So yes, we did not do any formal testing for publication bias.

BARTH RELLER: Dr. Fleming.

THOMAS FLEMING: Could we see slide 18. I actually have a comment and then a question leading into a question. As we formulate these margins, one fact that needs to be in the forefront of our thinking is that margins are specific to many different situations. They're certainly specific to the end point that you use and the timing of the end point. So, in these two Snodgrass studies here we're seeing a difference in the effects on spread of lesions and we see at two days here that there's a considerable difference and the estimates are probably about 28 percent. And you could, as has been discussing here, you could have a 10 percent margin discerning a new therapy that would come along that would be as affective as the affective therapy here, the antibiotic, or discerning an ineffective therapy that is just the same as UV light. And if you're using the two-day end point and a 10 percent margin, a new therapy that comes along that's as effective as the antibiotic would be able to rule out that you are ineffective and at the same time it would be able to detect an ineffective therapy. But, if you use this end point out here at five days then the resolution is the same in both arms and a new therapy affective therapy. So, timing of the end point matters as well as the end point matters.

So if you're going to use a margin, it has to be a margin against an end point that historical data shows is highly effective. And this is something that we'll have to keep in mind as we answer questions. Slide 50 leads to a question and actually is a question that comes up related to Katie's presentation as well.

SUMATI NAMBIAR: Slide 50?

THOMAS FLEMING: Slide 50, you went over very quickly, but we can come back to and we've done a lot of additional analyses to get at a critical point and that is when we do an non-inferiority margins in what populations do they apply. So not only do non-inferiority margins depend on the end point, and the timing of the end point, they depend on the population. And in Slide 50, you make the comment here for which there is you don't give the data in your oral presentation, but in your briefing documents you do, indicating that in skin abscesses even in major abscesses the evidence for treatment effect is far weaker than it would be in other settings and this has to be kept in mind.

You've also asked us to talk about uncomplicated versus complicated. And one of the issues is what is the definition of uncomplicated versus complicated. Katie, you went through that

very quickly at the beginning. And certain things are clearly and uncomplicated, minor skin abscesses, folliculitis, furuncles, impetigo was discussed in the uncomplicated. But you had mentioned, Katie, cellulitis, and it's my understanding that cellulitis could be either complicated or uncomplicated, and if that is correct, what is the formal definition that we're using for uncomplicated cellulitis?

SUMATI NAMBIAR: Dr. Fleming, these were the results of the skin abscess study that I mentioned in Slide 50. You said I hadn't provided the numbers, these are the results.

THOMAS FLEMING: Okay. But let me stay on the specific question. Is it correct that Katie, your slide went by very quickly and I don't think you gave us copies, but I think you had listed cellulitis as uncomplicated. And isn't it the case that it could be either and if so, what is your definition of uncomplicated cellulitis?

KATHERINE LAESSIG: I think that's correct that they are -- it may be somewhat unclear. You know the way these things are described in the guidance isn't necessarily set in stone so certainly it's appropriate for the community to discuss that kind of thing whether it's an uncomplicated skin infection or complicated.

THOMAS FLEMING: So essentially, we have discussed and you have indicated in your briefing document, that for minor skin abscesses, folliculitis, furuncles, there's simply no evidence of benefit at this point. And if you were to do a non-inferiority trial in uncomplicated you couldn't include those infections. You've given us some evidence for impetigo. think you've given us any evidence that would be a basis for a margin nor is there is a clear definition that I've yet heard as to what would characterize uncomplicated cellulitis. So essentially, the only data we've had here for any non-inferiority margin in uncomplicated would be impetigo; correct?

BARTH RELLER: Any comments from the infectious diseases clinicians as to how they would categorize cellulitis that was complicated versus uncomplicated? Dr. Pohlman.

JANICE POHLMAN: I think from a review standpoint the way you look at it -- and Katie was right, the guidance document isn't real specific, but in terms of host characteristics are one thing, immune status, the depth of infection, the dimensions, you know, the size of the lesion, I think those are all characteristics that lean more toward a complicated skin infection. However there is a gray zone.

BARTH RELLER: Dr. Cox.

DR. COX: So as we talked about, you know, there is going to be some overlapping between complicated and uncomplicated skin and structure infections. You know, one of the reasons why, you know, the impetigo data, you know, was helpful and the erysipelas data is helpful I think, is that it gives you some information about a treatment effect in a skin infection in -- over placebo.

You know, there are going to be differences as you move to other types of skin infections. You know, one of reasons we may not have data, you know, in the other skin infections is because they are more severe infections because of the consequences of delaying therapy. So, you know, thinking about uncomplicated skin infections, you know, there may be some relationships between impetigo and erysipelas and then also cellulitis. I mean as we move through different plains of tissue some of the organisms involved in the skin. So just one comment for consideration there.

BARTH KELLER: Dr. Rex.

DR. JOHN REX: I'm not going to comment right now on uncomplicated versus complicated because I think we are going to see a bit more data. I understand there's some more coming in a

presentation. But I do want to comment on the point that Dr. Fleming raises about time.

I agree with you that time is an important thing, but let me be clear -- and actually Dr. Nambiar made the point very nicely on Slide 47 that we actually incorporate time in every study we do even if you don't realize that you've done it.

The point is, and it's right there on the case report form, you think about what does the case report form look like in study? Does it -- do you or how do you approach a patient? Do you see the patient on day one and then come back two weeks later and say, "Hello, Mrs. Smith, how are you today?" And take no cognizance of the intervening interval? No you actually don't, you talk to Mrs. Smith every day. And Mrs. Smith only stays in the study as long as she is improving. If Mrs. Smith is not better by a few days into the study she's basically out

So as Dr. Nambiar points out, I believe it was this slide. Yes, it's right there. In present trials patients not improving get classified as failure and pulled out. So, we do actually measure. It's not quite the same. I agree it's a frustrating point. You've raised it well, it's good to say it that way. But let me be just very clear, that actually we do wash people out early. You can't succeed on day two. You can't

be a success, but you can be a failure. And maybe we have to work with that concept. So that's the comment I want to make.

THOMAS FLEMMING: But then you've changed the end point. Because you've changed the end point.

BARTH KELLER: Dr. Fleming, please. Go ahead.

THOMAS FLEMING: If you look at this as a way to somewhat correct for the inadequacy of addressing timing and you've change the end point. If the end point was preventing of spread and you take a patient off therapy at day two then the end point isn't prevention of spread, the end point is staying on therapy and/or prevention of spread. And so you've really conflicted the end point.

So the essence is to make sure that if you're using the data to justify a margin that that data reflects the nature of the assessment that you're going to make in your non-inferiority trial. And if you've change the end point in the non-inferiority trial, you have to come up with a new set of evidence to justify the margin for that new outcome.

BARTH KELLER: Dr. Rex.

JOHN REX: I'll rebut very briefly, we should discuss it in much greater length later on. But the point that I'm making is we made this point with fever during the CAP's workshop

previously. People don't get better, you know, they are not ultimately a cure if they don't resolve their fever, have their erythema go down, have the edge of their erysipelas stop from progressing. They don't get better.

Now I agree with you that it is not perfect. It's not what we want to measure, but we're going to have to work with the data that we do have and a resolution of progression of the edge is not cure of the disease. Now I understand that, you're saying that and I agree with you. However, you never cured if you don't do that and so it can be a way to trigger a failure. So it's a combination of medical and statistical analysis is required to jump this bridge and that's all I'm wanted to say right now. Thanks.

BARTH RELLER: Dr. Bennett.

JOHN BENNETT: Well one of the biggest challenges that this group has is definition. So I'd like to return to the question that was asked earlier, what is severe cellulitis? And I think we can look at that by asking what erysipelas is. We've been looking at studies here with erysipelas where there was a 10 to 15 percent mortality where people had positive blood cultures. So what's the difference between erysipelas and cellulitis? And the answer is not only a well defined edge,

which is often the mind of the observer, but whether it's rapidly spreading and accompanied by systemic signs. But this spreading stopped.

So I think one of the definitions here of severe cellulitis is when it is erysipelas. So looking at that distinction I think helps distinguish in my mind a simple cellulitis which is simply some red skin around a lesion or whether it's erysipelas.

BARTH RELLER: Barth Reller. To follow up on Dr. Bennett's point. Although it's not stated anywhere here, though implied in the Keefer studies, most of us would -- there's also the element of what the organism is and if it's spreading and it's Group A strep its erysipelas otherwise it may be just called cellulitis. Also in those historical definitions most would accept that when it's accompanied by bacteremia, which a fair share of these were, that's complicated and it's totally in concert with the remarks that you just made. The end point of spreading edge, how much of that redness and spread is owing to toxin that may or may not be affected at least by (inaudible) agent and that the spread continues even though the patient's fever is resolved and they're getting better. Any comments, Dr. Bennett from a long perspective on these clinical questions?

JOHN BENNETT: Well, you've made a good point and that is the patient is often getting better before the lesion actually stops even becoming -- spreading or becoming paler. So there is some inflammatory response that goes -- that is different from the patient's appearance. I was just trying to distinguish what is a complicated cellulitis. But the rapid spread -- I think you talk about it being due to Group A strep, but we usually don't know what its due to. Even though we do blood cultures they're usually negative and sometimes they're Group B strep or something else if we do get a positive blood culture. So I don't know if we can use Group A strep as part of the definition. I'm not sure you're implying that, but I don't find that helpful.

BARTH RELLER: No. Barth Reller. I wasn't implying it except that when we do get a positive blood culture then all of us think it's erysipelas. And perhaps Group A strep is more often accompanied by bacteremia in the clinical setting of cellulitis than other pathogens. Dr. Weinstein had his hand up earlier. You still -- Dr. Wiedermann is next.

MELVIN WEINSTEIN: Just one other thing on the complicated versus uncomplicated. I think in the clinical setting I am often concerned with the anatomic site and even

there with erysipelas if it's facial erysipelas where -- with a threatened compartment syndrome and an extremity that's a very different thing. The consequences of, you know, maybe the preservation of the treatment effect is more important there. Maybe we ought to be choosing different margins if the consequence -- potential consequences are more severe.

BARTH KELLER: Thank you. This afternoon we will also have time for the to and fro which is a very important part of this meeting in coming to grips with the precise definitions that will be required for the ultimate quantitative and Dr. Valappil for your presentation. We now move to presentation by Theravance on the applicants justification for the M1 margin.

ALAN HOPKINS: Good morning. My name is Alan Hopkins and I'm the senior Director of Biometrics at Theravance. This will be a joint presentation with Dr. Ralph Corey who is Professor of Medicine at Duke University. Dr. Corey is a recognized leader in research and treatment of staph aureus infections and has published extensively on the topic. We also have with us Dr. Gary Koch, Professor of Biostatistics at the University of North Carolina at Chapel Hill who contributed to these presentations. Dr. Koch also provided counsel on the

design and analysis plans for the Theravance studies. Dr. Koch is available to lend his expertise to the discussion as appropriate.

We are pleased to be here this morning to contribute to the discussion of non-inferiority margins for complicated skin and skin structure infections. The use of non-inferiority trials is critical for the successful development of new antibiotics for infectious diseases that may cause serious morbidity or mortality. Theravance has completed two Phase III clinical studies and has submitted an NDA for telavancin for regulatory approval. Today I will first present statistical considerations for the non-inferiority margin choice used in the two pivotal Phase 3 telavancin complicated skin studies. Then Dr. Corey will discuss the implications of the active control design in associated non-inferiority margin.

The use of an active controlled design begins with a demonstration of historical evidence that the active control has greater effect than placebo. This difference forms the basis for defining the non-inferiority margin which represents the maximum acceptable difference between the effect of the active control and an experimental drug. The telavancin trials provide an informative case study of the use of

non-inferiority margins to provide an estimate of treatment effect. In these studies, the active control is vancomycin. We shall demonstrate a 10 percent non-inferiority margin preserves more than half of the effect of the active control over placebo.

The actual observed margins in the two telavancin complicated skin studies were substantially less than the pre-specified 10 percent non-inferiority margin and thus assuring preservation of the effect of vancomycin over placebo. Active control trials have been the norm in complicated skin and skin structure studies because of the standard of care for cSSSI includes antibiotic treatment. Inadequate treatment is associated with increased morbidity and mortality. Dr. Corey will discuss specific complications in his presentation.

The Infectious Disease Society of America from whom you will hear later here today has recognized that the use of intravenous antibiotics is the standard of care for complicated skin and skin structure infections, especially MRSA.

There are a number of antibiotics approved for treatment of complicated skin infections using an active control design with the pre-specified non-inferiority margin.

Here is a list of recently approved antibiotics for the treatment of complicated skin infections based on a review of package inserts and FDA medical officer reviews. The key point here is that these studies were active control designs. Only three of these antibiotics, highlighted in yellow, are used today to treat complicated skin caused by MRSA the most common pathogen in this disease. Two of these antibiotics used a non-inferiority margin of 10 percent and one used a non-inferiority margin of 15 percent. There have been no placebo controlled trials in complicated skin and skin infections.

So this creates a problem for the estimation of the effect of the active control versus placebo. However, six controlled studies for uncomplicated skin were identified through a literature search. And so what we planned to do is use these uncomplicated skin studies as a bridge to conservatively estimate what the placebo rate would have been in complicated skin.

We think that for the complicated skin infections the placebo rate could be no more than the rate for uncomplicated skin infections. So in order to determine the

treatment effect of the active control over placebo we derived separate estimates of cure rates for placebo and the active control agent, vancomycin. The rates were derived by used a meta-analysis approach from historical data. Then the treatment effect of the active control is estimated using the difference between the vancomycin cure rate and the placebo cure rate. Five studies have been identified which serve as a basis for an estimate of the vancomycin cure rates in complicated skin infections. The vancomycin point estimates and confidence intervals are displayed graphically on the right side of the slide showing the range of activity demonstrated for vancomycin in these studies. Based on the fixed effects meta-analysis combining these results the estimated cure rate for vancomycin was 75.6 percent. The estimate is based on treatment of over 1,500 patients in these five studies. The meta-analysis result for vancomycin is consistent with data from the telavancin Phase 3 studies. The total of 900 patients in the telavancin studies were randomized to treatment with vancomycin. The difference between the pooled vancomycin response rates differed by less than one-half of 1 percent of the results we had from the meta-analysis. So we feel these data are consistent with the constancy assumption for the effect

of vancomycin over time. Six studies in uncomplicated skin and skin structure infections were identified to form the basis of the estimate for the placebo effect. These were randomized blinded studies in impetigo. The list includes the same studies that the FDA used in their presentation. The figure shows the estimates of the placebo rates in these studies. It can be seen that there's a fair amount of heterogeneity in the cure rates large response and one that had a zero cure rate.

These are two small studies and I think tend to cancel each other out a bit in the overall analysis. The differences may be attributable to the timing of the response assessment, the definition of cure or perhaps different patient populations. The summary row contains results for the meta-analysis. The overall estimate of the cure rate is about 6 percent. So now we are in a position to calculate the exact size for the active treatment. We do this by synthesizing an estimate of the difference between vancomycin and placebo. Using the historical rates that we already discussed we've come up with estimated vancomycin advantage over placebo of 2.8 percent based on the lower bound of a 95 percent confidence interval for the difference of those two sets of historical series of studies. We would expect the cure rates in complicated skin

would be at least as large or greater than this estimate. When translating this effect size into a non-inferiority margin we typically discount some proportion of the effect size so that the non-inferiority implies not only non-inferiority to the active control, but also preserves some level of benefit relative to placebo. This degree of discounting is usually a clinical judgment.

Now I would like to take a moment and discuss the design of the telavancin Phase 3 studies, their non-inferiority margin and overall results. The two Phase Three -- the two Phase 3 studies had identical protocols so each study was an active control design with an objective of non-inferiority. The trials were designed to be pooled. The goal of the pooling was to generate sufficient power for analysis of the superiority hypothesis in the treatment of MRSA infections.

We sought to enrich the patient population with MRSA. For design purposes we assume 40 percent of the patients enrolled would be MRSA infections. Patients were randomized to vancomycin or telavancin which was the experimental therapy in this case. Treatment lasted 7 to 14 days and a test of cure was done at 7 to 10 days after the end of therapy. A pre-specified

non-inferiority margin of 10 percent was used. The sample size was driven by the superiority hypothesis for MRSA, to achieve 80 percent power for superiority required 700 patients per study. This generated an even greater power to demonstrate non-inferiority in the individual studies yielding 98 percent power for the non-inferiority hypothesis. And predictably the results did demonstrate non-inferiority. For the all treated population both studies met a non-inferiority margin of five percent or less. We think that the best estimate of the overall treatment effect is the pooled estimate which was greater than zero favoring telavancin and had a lower limit for the confidence interval -2.2 percent which was far greater than the -10 percent that we set prospectively. So faced with the challenge of estimating the treatment benefit of vancomycin against placebo and in the absence of the placebo controlled trials it was necessary to use historical data from a less A 10 percent non-inferiority margin preserves more than half of this active treatment effect. The results from the telavancin studies were well within this region or this margin. And the pooled estimate of 2.2 provides the most precise estimate of the degree of non-inferiority observed in these.

Now Dr. Corey will present the medical basis for

defining non-inferiority margins and complicated skin infections.

RALPH COREY: Thank you, Alan. Good morning everyone. This is a daunting task to talk in front of such an austere group. Today, I would like to discuss some of the clinical issues involved with designing studies of patients with complicated skin infections. First I'll focus on the issues of placebo controlled trials and then I will give you my thoughts, as a clinician, on non-inferiority margins. But before I get started, let me give credit to the FDA, Brad Spellberg and the entire IDSA team for their terrific, absolute terrific reviews of the literature. It took a lot of time and effort and it's very helpful.

Staph aureus and Beta-hemolytic streptococci are the two most important organisms involved in complicated skin infections. Both of those organism are extremely very (inaudible) if left untreated.

Even Sir Alexander Ogston, the surgeon who discovered and named staphylococcus aureus, the golden staph, recognized its extraordinary capacity to cause harm. He talks about staph aureus causing acute superlative inflammation and the most virulent forms of septicemia pyemia. I can only

imagine his frustration at not being able to treat his patients effectively with these infections. The virulence of staph aureus was also -- staph aureus and Group A strep were always quite apparent to other physicians in the pre-antibiotic era.

Professor Domagk's daughter, Professor Domagk was a Nobel laureate, his daughter developed a severe strep infection after a needle stick in her father's laboratory. His new sulfa compound most probably saved her life. President Roosevelt's son, FDR, Jr., appeared to recover from a seeming fatal strep infection after receiving sulphanilamide. There wasn't much doubt about the effectiveness of these agents in this era. The virulence of these pathogens is also highlighted by this list of selected studies chronicling the outcome of untreated, treated staph aureus and Group A Strep.

I will not go through these each of these studies since this has already been done, but would like to simply point out the change in outcomes of the advent of antibiotics. Let's focus for a minute on Group A streptococcal subcutaneous infections.

Since there are no placebo controlled trials involving sulfa drugs or penicillin for the treatment of strep pyogenes, I would first like to show you some of the data concerning

sequility of this virulent organism from the pre-antibiotic era. And you've seen some of this before. Erysipelas is a rapidly moving group based streptococcal infection which is very differentiate from staph aureus. It frequently causes venous and capillary damage resulting in chronic swelling and recurrent infections in that area. In addition, death occurs in somewhere around six to nine percent if left untreated as was done by Lusk in 1922. In a series of 246 patients from the Boston City Hospital, as you heard streptococcal blood stream infections originated from a cutaneous source in nearly 25 percent. Of these patients, of these 61 patients 80 percent died.

Let me make this clear. If I'm a surgeon in the pre-antibiotic era like my hero Norm Bathum in China and I actually cut myself during surgery and I get a strep cellulitis which extends into my bloodstream, I die like Norman died.

Staph aureus is quaily virulent. Abscesses caused by staph aureus resulting in local scarring cellulitis caused by staph aureus results in chronic edema and fasciitis caused by staph aureus results in permanent damage, amputation even death. Similar to Group B strep bacteremia with staph aureus is deadly.

In a 122 patients from the Boston City Hospital again,

who developed staph aureus blood stream infection, nearly 50 percent had a skin infection as its origin. Interestingly, as was pointed out, the majority of these patients have what we know consider benign boils and carbuncles which were lanced. Mortality in this group was again over 80 percent. Unfortunately, there are problems with data from the pre-antibiotic era as has been pointed out.

First, it does not include any placebo controlled trials. Second, the landscape has changed, patients and conditions involved. There's less crowding, better hygiene, fewer injuries. On the other hand there's many, many, more invasive medical procedures and many many more frail patients, our elderly, our diabetic, our immuno-compromised. The bacteria too have changed. Strep has developed more toxins, but its resistance profile has remained fairly stable.

Staphylococcus on the other hand has developed into a much more resistant, a more virulent organism. As a result of these changes in both the environment and the organism, there have been dramatic changes in the infections that these virulent organisms caused in the 21st century.

Fortunately, Group A strep has not evolved any resistant mechanisms and antibiotics used in the 1940s are still

effective today, penicillin. Thus, the serious complications seen in the pre-antibiotic era have become rare. Necrotizing fasciitis accounts for only 300 fatalities per year in the United States. Similarly, bloodstream infection and endocarditis due to Group A strep are exceedingly rare. Fourteen endocarditis cases out of 5,000 we collected worldwide. I credit this remarkable change to antibiotics.

In contrast staph aureus is an ever present adversary. New virulences and new resistances have resulted in new complications. Rapidly developing abscesses are now extremely frequent. Though drainage is the mainstay of therapy, antibiotics do appear to increase cure rates as demonstrated by Chambers data with the double placebo controlled trial. Fasciitis has become primarily a staph initiated infection. And morbidity from this invasive infection is significant. Unfortunately, blood stream infections still occur in up to 50 percent of patients with complicated skin infections secondary to staph aureus. And as we know from Vance Fowler's publications, one-third of patients with blood stream infections develop metastatic complications including destructive infections of the spine, and joints and heart valves.

Clearly not all patients with complicated skin

infections secondary to Group A strep and staph aureus require antibiotics. Unfortunately, physicians like myself cannot accurately differentiate between patients who will and will not develop complications which makes paradigms for rescue therapy relatively impossible. Thus, the only solution is to treat the majority of patients initially who are suffering from complicated skin infections. I think it's crystal clear. Antibiotics are absolutely mandatory for the treatment of complicated skin and skin structure infections due to staph aureus and strep pyogenes. Until we are able to differentiate, with a high degree of certainty, who will and will not develop complications placebo controlled clinical trials in these patients are neither ethical nor possible.

Now let's turn to non-inferiority trials and margins. Our patients need options. In the reality of patient care in a patient's room antibiotic options are vital. And in order to provide these option if non-inferiority trials are essential. What about non-inferiority margins? Here's a summary of the efficacy estimates from the IDSA, the FDA on Theravancin. On the basis of this data, as well as my clinical and trial experience, I believe the targeted antibiotics are at least 20 to 0 percent more effective than placebo. Bottom line, for a new

anti-MRSA antibiotic to have a non-inferiority margin better than 10 percent compared to vancomycin makes me, and I believe the entire infectious disease community, confident that the drug is effective.

But finally please let us all remember the ultimate goal of these deliberations is not to create a new antibiotic approval hurdle, but to provide our patients with thebest possible therapeutic options. Thank you.

BARTH KELLER: Thank you Drs. Harris and Corey. The next presentation will be from the sponsor Targanta.

[Pause]

ALAN FORREST: Good morning. My name is Alan Forrest. I'm a senior scientist in pharmacometrics from the Institute of Clinical PharmacoDynamics within the Ordway Research Institute. I'm a research Professor at the Suny Buffalo Schools of Pharmacy and Medicine and I'm a special government employee to the FDA as a specialist in population Pharmacokinetic and PharmacoDynamic analysis. I'm here as a consultant to Targanta today to discuss the choices made regarding the non-inferiority margin that were used in the two pivotal trials for oritavancin. Next slide please.

This is a brief summary of the two trials. The first

of them, Study ARRD, was completed between 1999 and 2001. It was designed based on the 1992 FDA points to consider and employed a 50 percent non-inferiority margin. Its primary input was clinical efficacy and it had two weight-based groups 1.5 milligrams per kilogram of oritavancin and three milligrams per kilogram of the oritavancin compared to a non-inferiority type design to the outcomes for vancomycin/cephalexin. And as I'll show you, the non-inferiority margin was achieved within the pre-specified 50 percent margin.

The second study, ARRI, was performed in 2001 going into 2002. By that time there were new guidelines available and in communication and discussion with the FDA and based largely on the International Conference for Harmonization Guidance document E9 & E10, this study was designed. Again it was a -- the primary end point was clinical efficacy and a non-inferiority design to the same comparator vancomycin/cephalexin. And the non-inferiority margin used in this study was a ten percent and as I'll show you shortly this non-inferiority margin was also achieved in the pre-specified margin. Next slide please.

Here's a summary of the results for ARRD, ARRI. The original population was a clinically evaluable population. The intent to treat data were added because it's more common to look

at both of these in modern times so in the ARRD here are the response rates for the two oritavancin doses the response rates for the vancomycin comparators. And these are the point estimates for the treatment difference and the 95 percent confidence intervals of clinically evaluable and computed later the intent to treat arms. And again you look to the left hand limits to see whether they crossed over the 15 percent for this study. In ARRI again a simpler study. This study had a fixed doze of either 200 milligrams for subject weighing less than 110 kilos or 00 milligrams for those that were over and that was based on a population of Pharmakinetic analysis PharmocoDynamic justification based on the analysis of ARRD compared to vancomycin and the point estimates for the clinically evaluable and the intent to treat trial are shown here and with a lower limit at -- this is well within the pre-specified 10 percent margin.

Next slide please. We don't need to go through these. These are the four main areas of considerations that are reviewed and ICH-E10 and E9 considerations regarding the study design characteristics, quality of study oversight, the evidence for sensitivity to drug effect and defining an acceptable non-inferiority margin. We'll review all of these at least

somewhat and we'll have more emphasis on the latter two. Next slide please. Bit of the study design characteristics. For both of these studies vancomycin was chosen with an optional step down to cephalexin as a comparator. The pivotal studies were well designed and consistent with the current standards for definitions and such. The types of infections that were allowed are the classical infections and the definitions are available in the briefing document. But the types and the number of subjects for each type of infection that wound up in the studies cellulitis 29 percent. We'd like to stress that all of these were patients for whom IV therapy was considered in appropriate standard of care and they had substantial co-morbidities, and specifically allowed into these trials included the following co-morbidities diabetes, HIV, bacteremia, etc. So these were quite a complicated population of subjects.

Next slide please. At least two of the talks today have done quite an extensive review of the history. I won't spend much time on this. You can go back to the region prior to antibiotics and look to mortality rates in World War I where the debridement was the main treatment, mortality rates were 25 to 50 percent.

Across a number of impetigo studies between 1974 and

2008, reported response rates to placebo ranged from zero to 52 percent with a roughly pooled average of approximately 25 percent. Flores in '43, with some questions about that study, nonetheless reported in their placebo group a response rate of 50 percent compared to active treatment. Cruikshank in 1947 looking at two different definitions of response depending on which definitions you used had a placebo response rate of 15 or 1 and response to active treatment of 77 to 85. So this is a bit of the data we have for getting insight into a placebo response rate and for the treatment response rate of the comparator vancomycin. Since 2000, for example, there's been seven published Phase 3 clinical trials in complicated skin and skin structure infections which use vancomycin as the standard comparator. Looking to the ITT or modified intent to treat populations the vancomycin response rates ranged between 74 to 81 percent with a roughly pooled average of approximately 81 percent across those studies. Next slide please.

Another modern tool that can give us some insight into these questions of what is the drug effect, what is the placebo effect is population pharmacokinetic/pharmacoDynamic analysis. What we have in this figure came from a study by Preston, Drusano, et al. in JAMA, and as you see it was for the

drug legal levofloxacin given to 14 patient with a range of diseases. And we'll concentrate on this red curve which was a mix of complicated and uncomplicated skin structure infections. What we're looking at is a probability of clinical response on the Y axis as a function of this measure of drug exposure and activity, peak to MIC ratio for this study. And I call your attention to the two extremes in this relationship as this drug exposure approaches low values the acimatodic (ph) minimum response activity approaches zero was a little under 48 percent with this study with a mixed population of complicated and uncomplicated. And as drug exposure approaches optimal values the probability of positive outcome was approaching one. Next slide please.

Here's another study of this nature of population pharmacokinetic/pharmacoDynamic study. This one is in 76 patients that received tigecycline treatment of complicated skin and skin structure infections. The different color patterns are stratified upon the pathogens. Let's concentrated mainly on the strep pyogenes infection. And as you see in this study here we have probability of bacterial eradication is the response being modeled The measure of drug exposure and susceptibility that was used is AUC to MIC. And in this population of complicated

skin and skin structure as the drug exposure approaches zero the extrapolated placebo effect was a little under 20 percent.

Again, once you get passed in this case approximately 40 of these AUC to MIC units you're probability of a desirable outcome in this case of bacterial eradication was approaching unity. The other two curves, just to orient you, are the black curve are all of the red cases and with the cases with gram-negative infections added in and the blue curve are all the red plus black with the cases where anaerobes have been cultured and added in. And part of the purpose of population pharmacokinetic/pharmacoDynamic analysis is to tease out those factors, covariants, co-morbidities that -- and infecting bacteria and other factors which are important predictors of outcome. And you see that when you start merging things with disparate responses, what you tend to get is very flat non-informative curve. Next slide please.

So as we've heard and will hear today, the basis of a non-inferiority margin should be acceptable on both clinical and statistical criteria. We look to recent registrational studies and other historical data to help decide. And again we also made the choice to do the best job we can of gaining inference about the placebo effect from studies that give us some insight

into placebo effect and look to the best studies we have available for the comparator, in this case vanco, to give insight to the responses due to the active control.

We'll emphasize again that these complicated skin and skin structure infections are quite a diverse group of patients with varying response rates depending upon disease severity, sight of infection and underlying co-morbidities. And as a side issue we are looking at the merged data sets of these two Phase Three trials teasing out these factors that seem to have important predicted values for the likelihood of outcomes for oritavancin.

Our reading of the literature suggest that a placebo response rate of no more than 20 to 50 percent, and my judgment is 50 percent is falsely high for complicated skin and skin infection, it is a reasonable range. And a response rate to vancomycin of 80 percent is a very conservative estimate of its response response rate. It's the kinds of value you get more commonly in an intent to treat trial and its reduced because of the classification of a number of inevaluable cases and others as failures. In pharmacoDynamic studies the upper asymptote of these drugs including canco tends to be the 90 to 100 percent range.

Next slide please. So you certainly don't need me to go through these definitions with you again. We'll be reviewing the estimation of the M1 that small -- the treatment effect of standard therapy over placebo and two, the faction of M1 that we'll choose to protect against the possibility of And we have a table looking at a range of choices following. And the following are underlying assumptions of that table. Throughout the table we're considering 80 percent as a reasonable point estimate of the cure rate for standard therapy with vancomycin, again we feel that is conservatively low. And we'll look at a range of different possible cure rates to assign for placebo treatment. And as the most commonly used value fraction of M1 to uses M2, we'll look at a fraction of 50 percent and we've also computed an M2 as 66 percent of M1 for comparison.

Next slide please. So for all of cases where using 80 percent as a point estimate for the response rate to vancomycin the first column is a range of placebo response rates that we had discussed, going from 20 to 50 percent. The next column is a simple difference between of an 80 percent response rate to vanco and this placebo response rate.

The third column is an estimate of M2 as 50 percent of M1.

And the last column is an estimate of M2 using for contrast two-thirds M1. So looking to the most conservative estimate on this table for placebo response rate with a 50 percent estimate of difference between 80 and 50 or 30 and half of that 30 is 15 percent. If instead of looking to that highest extreme you look at one of these other numbers, and we just highlighted the midpoint of the range for comparison at the midpoint there was estimated placebo response rate of 5 percent. The difference between that 80 is 45 percent 50 percent as estimate of M1 will be 22.5 percent and even at two-thirds of that value we're still at 15 percent. Thus, the non-inferiority margin of 15 percent which had been used based on the guidelines available at the time that study was done for AARD and 10 percent which was used in the study that was more recent, both would have exceeded the necessary power to discriminate from placebo. Next slide please.

In conclusion both of these studies adhere to the major non-inferiority margin considerations that were contemporary to the time that they were designed and approved. The non-inferiority margin selected for study AARD, which was 15 percent, and AARI, which was 10 percent, are clinically relevant and statistically sound.

We'd stress that similar to many of the current

studies in the literature the population in these two studies were extremely ill and their responses were complicated by severe underlying co-morbidities. And we would conclude that the non-inferiority margin is to safely discriminate drug effect from that of placebo in seriously ill patients with the significant co-morbidities, non-inferiority margin of even 50 percent -- 15 percent is very conservative. Next slide please. And I'd like to acknowledge many people especially Evelyn Ellis-Grosse and Paul Ambrose and Sujata Bhavnani whohad a large part in helping to pull this presentation together. Thank you very much.

BARTH RELLER: Thank you, Dr. Forrest. We'll now have 20 minute break. We'll reconvene at 10:35 a.m. Also meeting topic during the break. Thank you.

[Break]

BARTH RELLER: Would all of the committee members please return to their seats. Our next 20 minute presentation will be by applicant number three, Arpida.

Dr. Khalid Islam.

KHALID ISLAM: Good morning, my name is Khalid Islam. I'm the former C.E.O. of Arpida and currently a member of the board of directors. On behalf of Arpida, I would

like to thank the agency for kindly inviting us to this meeting and for giving us this opportunity to present Arpida's position on the appropriateness of the NI margins in complicated skin and skin structure infections.

Our presentation will be in two parts. The first will deal with our rational and reasons for the proposed 12.5 percent margin for our two independent essentially identical studies. Additionally, I would like to point out one difference to some of the other studies we heard this morning. We have used linezolid as a comparator rather by vancomycin.

This first part of the presentation will be described by Dr. Charles Davis who has worked with us for several years as a statistical consultant. And we also want to go through a second part which is our thoughts and consideration on how we, as a scientific community, can better define NI margins and study design for the future. In this contexts we have worked closely with a group of Professor LJ Wei at Harvard and Professor LJ Wei will describe the proposal for these two future trials.

I'll now hand over to Dr. Charles Davis.

CHARLES DAVIS: Next slide please and the next one after that. Thank you, Dr. Islam.

My presentation will review relevant aspects of the ICH guidelines for selection of NI margins, the specific application to cSSSI and the use of linezolid as the comparator. According to ICH guidelines E9 the protomotion should clearly specify that testing for non-inferiority is the explicit intention. The NI margin should also be specified and the choice should be justified clinically.

The statistical analysis is generally based on the use of confidence intervals and for non-inferiority trials one sided competence should used. These roles assure the integrity of the analysis for regulatory purposes. ICH guideline E10 provides a clear understanding as to the definition of the NI margin. Note that there is no specification or assumption that the test treatment and the active control are equivalent.

The NI margin is instead specifying the potential degree of inferiority that should be excluded. This guideline also states that the NI margin should be identified based on past experience in placebo controlled trials of adequate design. And this is certainly one of the problems being grappled with in today's presentations. In their prospective specification of the NI margin Arpida followed ICH-E9 and E10 guidelines to the extent possible. The major difficulty however, is that there

specification of a 12.5 percent margin on the facts that NI margin on the facts that NI margin of 10 to 15 percent had been used in registration trials and that linezolid was thought to be the superior comparator for a variety of reasons. Let's start with two approaches for determining the NI margin for cSSSI trials. These aren't necessarily retrospective justifications since they were not presented in the protocols for Arpida studies.

One justification can be based on the results from a Phase Two dalbavancin trial. Note that estimation of antibiotic efficacy is based on the comparison between two doses and one dose; therefore, this approach is likely to be conservative when compared with placebo. In this study the cure rate in the two dose arm was greater than 0 percentage points higher than in the one dose arm. Preservation of 50 percent of the treatment of facts suggests that a 15 percent NI margin would be reasonable for a cSSSI study. One short coming is that the sample sizes were very small in this trial and as a result the confidence intervals for the cure rates in each of the two arms as well as the confidence interval for the difference between the two cure rates are quite wide. Although the sample sizes were small in the Phase 2 study a subsequent Phase 3 study using two

doses of dalbavancin demonstrated clinical cure rates that were similar to those reported in the Phase 2 study.

The second justification I will present is based on the comparison of the estimated cure rates for placebo and the active comparator. As I've already mentioned there are no placebo controlled trials. Based on the discussions I've been involved in with clinical experts I believe that it is reasonable to assume that the placebo cure rate in cSSSI is likely less than 50 percent and you've heard today that it could be 5 percent or less. On the other hand, it's possible to be more definitive with respect to the active control that was used by Arpida. Here's a justification that the linezolid cure rate is at least 75 percent. This slide displays cure rates from four studies. These were identified through a comprehensive search by an independent organization, the Analysis Group, and were the only four studies found that met the criteria being randomized, parallel group, head-to-head trials in cSSSI. Using the results from these four trials the pooled estimate of the linezolid cure rate is 77 percent with a 95 percent confidence interval that has a lower limit of 75 percent. It's also reasonable to augment this using the linezolid results from Arpida's two trials. Arpida trials were also randomized,

parallel group studies in cSSSI. If all six studies are used the lower bound of the 95 percent confidence interval for the linezolid cure rate is 77 percent, and note that these are based on the ITT results.

A second source of data is based on a recent meta-analysis that was published by Falagas et al., in the Lancet Infectious Diseases. Using the results provided from eight studies in skin and soft tissue infections, the pooled cure rate for linezolid literature is 90 percent and the lower proceeding results can then be applied to determine the NI margin based on preserving 50 percent of the difference between placebo and the active control. As one would expect, the resulting margins are highly dependent on the assumed placebo cure rate. However, a conservative assumption of a 25 percentage point difference between placebo and active control would justify a 12.5 percent NI margin. Given the state-of-the-art and regulatory guidances in 2004 for trial design assumptions for cSSSI, a 50 percent placebo cure rate was not an unreasonable assumption.

Lets now address the question as to whether there is evidence to support a different NI margin if the linezolid is the comparator. As background, it's important to

note that vancomycin is an appropriate choice for MRSA infections. However, for the treatment of infections due to MSSA semi-synthetic penicillins are superior compared to vancomycin. In addition, linezolid is approved for infections caused not only by MRSA but also MSSA and streptococci.

The four studies identified by the analysis group were previously used to estimate the linezolid cure rate. These studies can also be used to estimate the difference between linezolid and the comparator. The cure rates in the linezolid and comparator arms from the four studies are displayed here. And to summarize, linezolid was shown to be more efficacious than teicoplanin by four percent; dalbavancin by six percent and vancomycin by five percent. In addition, linezolid was shown to be efficacious than semi-synthetic penicillins by four percent and as mentioned, semi-synthetic penicillins are superior compared to vancomycin.

The results of these four trials can be pooled to obtain a weighted average estimate of the difference between linezolid and the comparator. The point estimate of this difference representing the superiority of linezolid is five percent and the lower limit of the 95 percent confidence interval is 2.1 percent. The same type of calculation can be

carried out using the data provided in the Falagas et al analysis yielding a similar estimate of the superiority of the linezolid. In this case, the point estimate is 4.5 percent and the lower limit of the 95 percent confidence interval is 2.2 percent. Both analyses indicate that linezolid provides cure rates that are estimated to be approximately five percentage points higher than provided by the comparator. In addition, one can be 95 percent confident that the superiority of the linezolid is greater than two percentage points.

To conclude my portion of this presentation based on the totality of the evidence that's been presented an NI margin of at least 12.5 percent is reasonable especially in populations with significant MRSA. Based on the results of randomized parallel group trials a larger NI margin is reasonable when choosing linezolid which is approved for MRSA, MSSA and streptococci rather than vancomycin as the active control. Professor Wei will now discuss a proposal for future NI trials in cSSSI.

First, I really appreciate Arpida give me five minutes for general discussion not to justify their NI margin. I asked Dr. Islam and the leadership in Arpida, could I have more than five minutes they said, "Do you understand in our

business one minute is equivalent to $1 million."

So, our group at Harvard actually just started a program two years ago called a program of Quantitative Science in Pharmaceutical Medicine. The goal of that program is actually try to have a dialogue among FDA equivalent and the industry and academic so we can exchange idea how to speed up getting drug approved -- safe drug approved.

A group of us actually working on this non-inferiority trials, the conceptual levels also methodology, our academic dean Jim Weher (ph) wrote a very nice paper actually published in New England Journal of Medicine. He's actually saying the NI trials have a two sided stories and unfortunately we only consider one side of story.

Next one, please. Next one, please. So here's sorry you go too fast. I know I only have five minutes, but. So there are two-sided stories actually. First, you asked yourself if you have -- you choose a active control supposedly it's the best control you can have right now. Say cure rate is 80 percent and then you say you're going to give 10 or 15 percent margin. You ask yourself why, why do you want to give up efficacy for 10 or 15 percent? Now the problems of course, the members around the table knows much better than I do so this is a trade off.

