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63rd MEETING

OPEN SESSION

Thursday, February 19, 1998

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P R O C E E D I N G S

DR. RELLE: I would like to welcome everyone to the 63rd Anti-Infective Drugs Advisory Committee meeting of the FDA. I am Dr. Barth Reller and will be the Acting Chair for this session.

I would like to begin the meeting by turning the microphone over to Ermona McGoodwin, our executive secretary of the Advisory Committee for the conflict of interest statement.

We will then introduce all of the members and consultants of the committee and begin with an introduction by Dr. Gary Chikami, the Director of the Division of Anti-Infective Drug Products. Then, we will have background presentation by Dr. Barbara Murray, who is a consultant to the committee for this morning's presentations. Then, we will go to the sponsor presentations and to the FDA presentations before lunch.

During and after the presentations, we will have questions focused on the data presented. The more general discussion and questions related to interpretation of all the material presented will take place in the open discussion this afternoon.

Ermona.

Conflict of Interest Statement

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

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

In accordance with 18 U.S.C. Section 208(b)(3) and Section 344(n)(4), full waivers have been granted to Drs. Norden and Parsonnet.

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

We would like to note that two of the committee participants had previous involvements related to Synercid and trovofloxacin that we believe should be disclosed. FDA believes that it is important to acknowledge these participants' involvements, so that their participation may be objectively evaluated.

In the past, Dr. Norden treated a patient with Synercid under an emergency care protocol. Dr. Soper spoke

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at a trovofloxacin symposium last year. He has no future engagements scheduled.

With respect to FDA's invited guest speakers, Drs. Barbara Murray and Gordon Archer, they have reported interests which we believe should be made public in order to allow the participants to objectively evaluate their comments. Dr. Murray would like to disclose that she receives contractual support from Bayer and Pfizer. She also lectures at various academic institutions which receive funding from Pfizer and Merck. In the past, Dr. Murray has served on an occasional advisory board to Rhone-Poulenc Rorer, Roerig, Pfizer, Bristol Myers Squibb, and Glaxo Wellcome.

Dr. Archer would like to disclose that he has a grant from Bristol Myers Squibb Research Foundation and has consulted for Bristol in the past two years. Dr. Archer has also reported that he occasionally lectures for Rhone-Poulenc Rorer and Bayer and is on the Scientific Advisory Board of PRI Ortho-McNeill.

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

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the record.

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

Thank you.

DR. RELLER: I would next like to go around the table and have introductions of the invited guests and members of the committee.

Dr. Archer.

DR. ARCHER: I am Gordon Archer. I am Professor of Medicine and Microbiology and Chief of the Division of Infectious Disease at Virginia Commonwealth University in Richmond, Virginia.

DR. MURRAY: Barbara Murray, similar title at the University of Texas Medical School in Houston.

DR. SOPER: I am David Soper. I am a Professor and Director of Gynecology and also a Professor of Medicine at the Medical University of South Carolina.

DR. CHRISTIE: I am Celia Christie. I am an Associate Professor of Pediatrics at the University of Cincinnati, College of Medicine. I am a member of the Division of Infectious Diseases and Epidemiology at the Children's Hospital Medical Center in Cincinnati.

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DR. WITTNER: I am Murray Wittner, Professor of Pathology, Parasitology, and Tropical Medicine at the Albert Einstein College of Medicine.

DR. CHESNEY: My name is Joan Chesney. I am a Professor of Pediatrics and in the Division of Pediatric Infectious Diseases at the University of Tennessee in Memphis.

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

DR. RELLER: Barth Reller, Professor of Medicine and Pathology, Division of Infectious Diseases, and Director of Clinical Microbiology at Duke University.

MS. McGOODWIN: Ermona McGoodwin, FDA.

DR. NORDEN: Carl Norden, Professor of Medicine, University of New Jersey Medical School and head of Infectious Diseases at Cooper Hospital in Camden.

DR. PARKER: Donald Parker, biostatistician, University of Oklahoma Health Science Center.

DR. JUDSON: Frank Judson, head of Infectious Diseases at Denver Health Medical Center and Professor of Medicine at the University of Colorado.

DR. CHIKAMI: I am Gary Chikami. I am the Director of the Division of Anti-Infective Drug Products, FDA.

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DR. ROBERTS: Rosemary Roberts, Medical Team
Leader, FDA.

DR. RAKOWSKY: My name is Alex Rakowsky. I am a
medical officer, FDA.

DR. THOMPSON: I am Susan Thompson, also a medical
officer at the FDA.

Issue: NDAs 50-747 and 50-748 quinupristin/dalfopristin

Synercid--Rhone-Poulenc Rorer Pharmaceuticals

Introduction

DR. RELLER: Dr. Chikami.

DR. CHIKAMI: Thank you, Dr. Reller, and good
morning. First of all, I would like to welcome our
committee and their consultants and the pharmaceutical
sponsor to this, the 63rd meeting of the Anti-Infective Drug
Products Advisory Committee.

Before we start, I would like to particularly
welcome four new members to the committee. We certainly
appreciate their willingness to give of their time and their
expertise as we deliberate many of the thorny questions that
come before us as a regulatory agency. They are:

Dr. Patricia Chesney, who is Professor of
Pediatrics at the University of Tennessee. Her areas of
expertise include pediatric infectious diseases and

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microbiology; Dr. Celia Christie, who is Associate Professor of Pediatrics at the University of Cincinnati Medical College. Her areas of expertise include pediatric infectious diseases and epidemiology.

Dr. David Soper, Professor of Medicine in Obstetrics and Gynecology at Medical University of South Carolina, whose areas of expertise include Ob/Gyn and infectious diseases.

Finally, Dr. Murray Wittner, who is Professor of Pathology, Parasitology, and Tropical Medicine at the Albert Einstein College of Medicine. His areas of expertise are pathology, parasitology, and tropical medicine.

In addition, I would like to welcome Dr. Diane Murphy, who joins us from the University of Florida, Department of Pediatrics. As of March 5th, she will be taking over as the Director of ODE-4, which is the office in which the Division of Anti-Infective Drug Products resides.

In July of 1996, there was a meeting of the Anti-Infective Drug Products Advisory Committee to discuss issues surrounding antibiotic resistance and the role of the FDA in addressing this problem. Many issues were discussed at that meeting and clearly the FDA has a role in the partnership with other public health agencies, such as the CDC, academia, and industry, in addressing this important

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public health problem.

More specifically, as a regulatory agency, the FDA has an impact on the development of products meant to treat infections due to resistant organisms. Over the years, general mechanisms have been developed in the regulations for addressing the needs for developing products for serious and life-threatening illnesses, which these sorts of infections would certainly fall under.

They include Subpart E of the IND regulations, the Orphan Drug law, and mechanisms for access to investigational agents, such as the treatment IND. Certainly, as you look at the history of the development of the product before us today and the A application, many of these mechanisms have been put into place.

In particular, the spirit of the Subpart E regulations involving early and close interaction between the division and the pharmaceutical company in agreeing on the development plan for the product and also the use of the treatment IND to provide access to the agent during the investigational process.

The committee in July also discussed a number of other issues which impact on the development of these products. Some of them include specific organisms which present particular problems for drug development, such as

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pen-resistant Strep pneumo, methicillin-resistant Staph aureus, and vancomycin-resistant enterococcus infections, the quality of clinical data necessary to adequately determine if a drug is effective for the treatment of such infections.

Some of the factors which may impact on those decisions include the overall incidence of infection with these organisms, the specific site of infection to be studied, and whether based on the overall incidence it is reasonable to pool data from different sites of infections with the same organism, and also whether or not other active agents are available to treat the infection that is being studied.

I think these are some of the issues that will be evident as you consider the data from the new drug application for Synercid that will be presented today by the sponsor and by the FDA reviewers. We look forward to the presentations and to the committee's discussion.

Thank you.

DR. RELER: Thank you for our road map for today.
Gary.

Next, we will have Dr. Barbara Murray, who is a consultant to the committee, to present the microbiological background for the topic under discussion.

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Dr. Murray.

Background

DR. MURRAY: Thank you. We will probably need the lights down a little bit.

[Slide.]

I was asked to give an overview of enterococci in general with certainly a focus on VRE, and to go through a little bit of background, the name enterococcus derived from an early publication in French describing a gram-positive coccus of enteric origin in 1899, an isolate the same year, which was probably a hemolytic enterococcus was isolated from a patient with endocarditis.

A few years later the name *Streptococcus faecalis* was first used also to apply to an isolate from a patient with endocarditis. The role of this organism or organisms similar to enterococci in endocarditis was well established over the next 20 years.

[Slide.]

From approximately the mid-1930s to the mid-1980s, enterococci were placed in the genus *Streptococci* and most of us with a few gray hairs knew them as group D streptococci. The enterococci were distinguished from the non-enterococcal group D streptococci like *Strep bovis* by certain biochemical tests. The most common organisms were

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Streptococcus faecalis, which accounted for approximately 85 to 90 percent of infections during that time period, the second most common being *Streptococcus faecium*.

[Slide.]

In about the mid-1980s, based on genetic typing and testing, enterococci were decided to not be closely related to streptococci and were moved into their own genus referred to as *Enterococcus*. The species names were retained and a number of new species were identified.

Again, up until the era of vancomycin-resistant enterococci, *Enterococcus faecalis* was the most common organism, accounting for 85 to 90 percent of infections, with *E. faecium* being second. Most of the ones on this side have caused clinical infection, many of this side have not been reported as a cause of infection in humans.

[Slide.]

In addition to the role of the enterococcus as a true pathogen in endocarditis, it has been increasingly recognized since the mid-1970s as a cause of opportunistic infection or nosocomial infection in superinfection in patients in the hospital and particularly those on antibiotics.

This role as a nosocomial opportunist was coincident with, and probably related to, the antibiotic

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resistance of the enterococcus, particularly their resistance to third-generation cephalosporins, whose use increased in the late 1970s. The resistances that bother us most today include the three here that I will spend a little more time on in the next few slides.

Now, the enterococcus really presents two problems, one that is more germane to the discussion today, and that is, in today's world, can we even inhibit them. This is mainly a problem with the species *E. faecium* when highly resistant to ampicillin and vancomycin, and in this country, such isolates that have these two properties, are often resistant to most or all other antibiotics.

The enterococcus has another problem, and that is, even if we can inhibit it, can we kill it. This is actually mostly a problem with the other species, *E. faecalis*, when it causes endocarditis, although certainly if *E. faecium* causes endocarditis--which it can--this again becomes a problem.

[Slide.]

Now, looking at its role in nosocomial pathogens, these are somewhat old data, but the enterococcus has been fairly consistently, over the past decade or two, been reported as the second to third most common organism recovered from nosocomial infections, as shown here.

[Slide.]

Now, those nosocomial infections include urinary tract infections. The enterococcus is a common cause of nosocomial urinary tract infections, although not of urinary tract infections in otherwise healthy individuals, typically women.

It is typically found in pelvic and intra-abdominal wound infections, frequently isolated, but other organisms are more important and the necessity to treat empirically early on in such infections, mixed infections, is still somewhat controversial.

[Slide.]

The organism can cause spontaneous peritonitis, particularly in individuals with cirrhosis and ascites, nosocomial bacteremia. Neonatal sepsis can occur in two versions. One is in the normal neonate, it is a distant third in some studies behind E. coli and group B streptococcus as a cause of neonatal sepsis, but more often it causes sepsis in this population in the very sick, intensive care unit hospitalized baby.

CNS infections occur. They only rarely occur in individuals who have not had a CNS manipulation, injection, surgery, et cetera.

[Slide.]

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Now, treatment of certain enterococcal infections has always been somewhat problematic and debatable, and I will just give you one example here, and that is enterococcal bacteremia. The source is often one of various possibilities. It is often polymicrobial.

It has been associated with high mortality known to occur more in the more severely ill patient, but also appears to independently increase mortality in some, although not all, studies. But the therapy remains to this day really unknown, should we treat short, should we treat long, should we treat as endocarditis, can we use a single agent, or does it need to be a combination of, say, penicillin plus an aminoglycoside.

Recommendations, both anecdotal and published, would range from no therapy to four weeks depending on the number of not well defined clinical factors including severity of the bacteremia, two or more positive blood cultures, source, nosocomial versus community, the evidence that the organism is actually causing infection, and possibly the presence of severe underlying disease, but this remains a clinical dilemma to this date as to how each individual patient should be treated.

[Slide.]

Now, the problems of enterococci really relate,

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many of them, to its antibiotic resistance, its resistance naturally or inherently to many of the agents we would use for other gram-positive organisms like staph and strep, so it is resistant to the anti-staphylococcal penicillins, cephalosporins, clindamycin typically.

[Slide.]

Now, another problem that appears to be typical of enterococci is its failure for a single drug like penicillin or vancomycin to adequately cure endocarditis, a response rate of at best 40 percent observed way back in 1954.

Combination therapy for many years has been known to be better and that is the standard of therapy for enterococcal endocarditis, that is, penicillin or vancomycin plus an aminoglycoside.

[Slide.]

The explanation for that need is probably seen here where the ability of penicillin to inhibit the MIC of enterococci is less than that of its ability to inhibit other streptococci, but particularly, the MBC, the ability of penicillin to kill the enterococcus is much less than against other streptococci, and as you know, endocarditis is one of those infections where we need a killing regimen.

[Slide.]

The efficacy of the aminoglycoside is illustrated

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here. This is the killing effect, marginal at best, of penicillin alone in a time-kill curve, the effect of adding the aminoglycoside produces more rapid and complete killing.

[Slide.]

Now, moving from the intrinsic resistance to the acquired resistance, the big three including high-level resistance to vancomycin, beta-lactams, and aminoglycosides are our big problem. We really did not care about these resistances to any extent in the past because they weren't considered enterococcal therapies.

We became interested in these possibilities only after these resistances emerged, and it turns out that most organisms with these resistances have many, if not all, of these resistances, as well.

[Slide.]

Again, one that does not pertain so much to today is the problem of high-level resistance to aminoglycosides, which eliminates that synergistic bactericidal effect I showed you. Just to illustrate the problems of the organisms, what do we do if a patient has endocarditis with such an organism with high-level resistance to all aminoglycosides? We don't know.

Some have recommended continuous infusion ampicillin. Many of us, when called, will say try extra

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long therapy, instead of four to six weeks, 10 to 12 weeks, rather than empiric, off-the-cuff based on some animal model data, but very little human data or valve replacement for relapsing disease. It is a difficult infection to deal with.

[Slide.]

The second of the big three high-level resistance to beta-lactams, the species, *Enterococcus faecium* has been known for many years to be more resistant to penicillins than *Enterococcus faecalis*.

Until about 10 years ago, the average *Enterococcus faecium* would be inhibited by between 16 to 64 mcg/ml of penicillin although high-dose therapy could still achieve this, more recent isolates in the past decade are even more highly resistant, not inhibited by upwards of 256 mcg/ml in some instances.

[Slide.]

Moving now to the vancomycin-resistant enterococcus problem, the initial descriptions were from Europe. The initial isolates were from 1986 in several European countries.

[Slide.]

In the United States, there was an early isolate in 1987, but the big onslaught was in the late 1980s where a

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number of isolates in the northeast part of this country were observed, followed by the Midwest.

Now, an interesting observation made in several studies, both the CDC and a report here by Ron Jones, and that was in 1992, 23 percent of hospitals surveyed had VRE, and they were all east of the Mississippi, but over the next two years, there was a progressive appearance of VRE, so that 61 percent of the same hospitals had VRE by 1994 including states west of the Mississippi.

[Slide.]

This is a slightly outdated CDC slide showing VRE rates as of 1994, the percent of the enterococci resistant to vancomycin. The data have not changed too much over the next two years, a little bit of an increase.

So, whereas, in their survey, hospitals, approximately 14 percent of enterococci were vancomycin resistant in 1994, and a little bit higher in '96, that is not true of the entire country. There are certainly some regions that are down in this area, Houston being one of them, even in 1998.

[Slide.]

Now, something I refer to as the peculiar and perverse nature of vancomycin resistance is that it has appeared preferentially in the species *Enterococcus faecium*.

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I mentioned that prior to vancomycin resistance, *E. faecalis* predominated about 9 or 10 to 1 among clinical isolates, but vancomycin resistance has appeared preferentially in this species, about 10 to 1 in several studies.

[Slide.]

Now, why is that perverse? It is because I mentioned this as the ampicillin resistance species, and unfortunately, vancomycin resistance has in this country often appeared in that subset of *E. faecium* that is highly ampicillin resistant, and this was a so-called bad bug in Philadelphia pointing out the high level resistance to both of those antibiotics, and that really is the problem.

[Slide.]

I have two cases right now that I wanted to mention to sort of illustrate the problems. This was a 23-year-old woman with AML, known to have fecal colonization with vancomycin-resistant enterococci for six months, and that is very common. The organism may be colonizing and doing no damage for quite a long period of time.

On her final admission for leukemia, she presented with fever, chills, rapidly became septic in appearance, urine culture was positive for VRE, as were two sets of blood cultures drawn hours before her death from sepsis while receiving vancomycin and ceftazidime and gentamicin, a

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standard that would be accepted in most locations, to which the organism was completely resistant.

So, this illustrates the problem. Now, I don't know that her organism was resistant to everything, but it was certainly resistant to all the standard therapies that she was given at the time of her demise.

[Slide.]

Another case which has not been published, but was one I was involved with, was a 29-year-old man, not quite such a severe illness as other patient, with paroxysmal nocturnal hemoglobinuria and Budd-Chiari syndrome, began to have positive blood cultures for VR E. faecium in late 1994 and had them on numerous occasions over the next six months.

Initial echocardiograms were not definitive for endocarditis and it was thought that the patient had an infected clot in the inferior vena cava. In fact, thrombolytic therapy seemed to dissolve that clot and blood cultures were transiently negative.

The patient received a variety of antibiotics, vancomycin to which it was resistant, ampicillin to which it was resistant, minocycline to which it was susceptible, rifampin to which it became resistant, gentamycin to which it was resistant. Some led to transient clearing of the bloodstream, but then would come back. The patient also

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received teicoplanin to which it was susceptible, but the organism developed resistance.

The patient was treated with minocycline for a prolonged period of time and finally discharged, but admitted four weeks later with positive blood cultures and died. Autopsy showed endocarditis with a vegetation of 10 cm x 3 x 2, which is a huge vegetation.

This illustrates an organism that could be inhibited. There was minocycline, but this infection, endocarditis, did not respond and the patient went on to die after a six-month illness.

[Slide.]

So, what do we do about VRE? The problem again is that the new resistances have been added on to the background of a number of acquired and intrinsic resistances.

[Slide.]

This is a slide I have used for grand rounds, and I say resistance to vancomycin, what do we do? Test whatever you can think of, for example, tetracyclines, chloramphenicol, and consider using whatever looks active, and that is the state-of-the-art, as you know.

Now, other than Synercid, which you will hear about today, these combinations in individual agents have

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primarily been looked at in either anecdotal cases, animal models, or just in vitro, and there are certainly no firm data for any of them except if the organism is an *Enterococcus faecalis*, ampicillin would certainly still apply, and even some of the faecium with moderate resistance, we have used ampicillin at 20 grams a day for an endocarditis patient with an MIC of 64 with an aminoglycoside, and that patient responded.

Now, some of these combinations like ciprofloxacin, gentamicin plus rifampin looked very active in the test tube and in the animal model if the organism was susceptible to each of these, but few VRE are susceptible.

In addition to combinations like cipro and novobiocin, novobiocin has been given with a tetracycline, and it is difficult really to say how efficacious it was. Newer fluoroquinolones have much enhanced gram-positive activity against enterococci, as well as other organisms, but if the organism is already ciprofloxacin resistant--which many are--these agents have decreased activity in the test tube.

[Slide.]

Other things on the horizon include some new glycolipopeptide-like antibiotics. The elongation factor TU inhibitors I have not heard much about in the last few

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years. Glycyl cyclines and oxazolidinones have activity against enterococci. They both are likely to be bacteriostatic, and not bactericidal.

[Slide.]

Now, of the sort of published reports of anecdotal and small collections of therapy, there is a problem with assessing how the antibiotics have acted, and one of the problems is the frequency in enterococci of severe underlying disease.

[Slide.]

We have often said sick patients get enterococci, and now we say and sicker patients get VRE. There is also publications suggesting that sick patients get *E. faecalis* and sicker patients get *E. faecium* even when it's not vancomycin-resistant.

This paper talked about, for example, patients with VRE bacteremia have been hospitalized an average of 26 days, received antibiotics for most of those, had a high rate of accompanying hematologic malignancy, respiratory, or renal failure and other severe diseases.

[Slide.]

That same paper looked at the percent of patients who died after VRE bacteremia from 24 hours to 21 days. These were not, by and large, thought to be attributable to

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enterococci necessarily, but about 60 percent died just reflecting the severe underlying disease of that population.

[Slide.]

Now, does VRE bacteremia, for example, actually affect mortality? One study suggested that--well, first of all, it pointed out that independent risk factors for getting VRE were, as I alluded to, more severe illness, receipt of antibiotics.

In this study after controlling for the APACHE II score and gender, patients with VRE versus vancomycin-susceptible bacteremia did not have a significantly increased mortality. Now, that study, however, allowed as few as one positive blood culture and was not in the most severely ill population.

[Slide.]

Another study found a different result. Vancomycin resistance was an independent risk factor for enterococcus-associated mortality. This was on a liver transplant service, liver transplant being a known high risk for *E. faecium* even before VRE, and had a stricter definition with two or more positive blood cultures or one-plus organism at a sterile site. In this case, VRE was associated with increased mortality.

[Slide.]

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Other problems with assessment of some of the reports in the literature include the fact that we don't know the spontaneous resolution rate of certain instances when enterococcus is present.

Many of the reports are complicated because there is drainage or debridement, removal of catheter, a recovery of white blood cells, or other antibiotics are given which might have sub-MIC effects or might eliminate other organisms which might be helping let the enterococcus persist.

[Slide.]

Again, just some examples showing you the problems that the clinician faces in trying to decide what to do with the VRE infection. This was a study recently in the Archives of Internal Medicine of a not too sick population, only 4 of 28 died, and they were thought not to have died from their VRE, but 4 of 6 bacteremias resolved when the line was removed, 1 of 6 resolved with line removal plus a drug, and 1 of 6 persisted and probably had an infected ventriculoperitoneal shunt.

Of the surgical site infections, 8 of 8 resolved with debridement and local care, although 2 also got a drug which might have some enterococcal activity.

[Slide.]

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Of pelvic abscesses, peritonitis, soft tissue infections, 3 of 7 resolved with drainage or debridement without drugs likely to affect VRE. The other 4 also resolved, but the patients got some drug likely to be active.

[Slide.]

So, then, when one looks at a report of chloramphenicol therapy for vancomycin-resistant enterococci, one realizes how difficult it can be to decide if this drug worked. There were 16 patients. They had multiple severe underlying diseases, 9 died during the studies, over half of the population, 8 of 14 improved with chloro, but 4 of those also got rifampin and 13 underwent drainage.

[Slide.]

I would like to finish with two cases that again show the difficulties of these infections.

This is a patient who developed multiple liver abscesses after the second liver transplant, was pure VRE and VRE bacteremia. At subsequent retransplantation for the liver, pus from the liver grew VRE and *Candida albicans*, the patient's infection resolved with liposomal amphotericin directed against the *Candida* and had no recurrence. So, this was an example of if you could cut out the liver, the

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entire infection, you could cure the infection. Would antibiotics have helped in that instance? Perhaps.

[Slide.]

Another patient following retransplantation for chronic rejection and hepatic artery reconstruction, this patient developed pyrexia and six sets of positive blood cultures for VRE, was resistant to a variety of antibiotics. Debridement of necrotic parts of the liver and intra-abdominal fluid grew VRE over the next two months. A large collection in the area of the resection was drained at laparotomy and showed persistence of the VRE.

Finally, with biliary reconstruction and prolonged treatment with piperacillin plus gentamycin to which the organism was resistant, there was gradual resolution, but clearly causing a role in this patient's illness.

[Slide.]

Well, I have talked about VRE. The other concern, of course, about this resistance is that it is on mobile transferable elements and there is great concern that it will transfer to methicillin-resistant Staph aureus, to penicillin-resistant pneumococci for which we now use vancomycin usually in combination with other agents, to viridans and streptococci, some of which are totally resistant to penicillin with MICs of 128 or greater, or to

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some of the other gram-positive organisms for which vancomycin has been used.

[Slide.]

Evidence for how far vancomycin resistance has spread in nature, the Van A genes have been found in a variety of enterococcal species, as well as some other gram-positive organisms. Van B has been found in a smaller distribution of organisms, but has been found in *Streptococcus bovis*, supporting our concern for spread of this resistance into other gram-positive organisms.

With that, I will end. Thank you.

DR. RELLER: Dr. Murray, thank you for setting the stage superbly for the subsequent discussions.

Are there any questions for Dr. Murray?

If not, I would next like to ask Dr. John Savarese to step forward and introduce the sponsor presentations from Rhone-Poulenc Rorer.

Dr. Savarese.

Sponsor Presentations

Rhone-Poulenc Rorer

Introduction

DR. SAVARESE: Good morning. I am Jack Savarese, Director of Regulatory Affairs for Anti-Infectives at

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Rhone-Poulenc Rorer.

[Slide.]

Today's presentation is on Synercid, which is the first intravenous antibiotic of the streptogramin class for the treatment of serious gram-positive infections in hospitalized patients.

[Slide.]

I will begin RPR's presentation with an overview of Synercid and a description of the indications submitted to FDA for approval.

Dr. Michael Edmond will review the epidemiology of serious gram-positive infections.

Dr. David Gilbert will follow and address the medical need for additional anti-infectives to treat serious gram-positive infections especially those caused by resistant pathogens.

The microbiologic profile and clinical pharmacology of Synercid will be reviewed by Drs. Nadler and Rhodes respectively.

Dr. Talbot will then present RPR's analysis of the clinical trial data submitted to FDA in support of the claims in labeling.

[Slide.]

Synercid is novel in having two chemically

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distinct components: quinupristin and dalfopristin, which have a synergistic antibacterial effect which is bactericidal against many pathogens. Synercid will be the first available alternative to vancomycin in 30 years.

Clinical trial data to be shown today will demonstrate Synercid's effectiveness in treating serious gram-positive infections especially those caused by methicillin-resistant Staphylococci and vancomycin-resistant *Enterococcus faecium*.

[Slide.]

Streptomyces produce Group A and Group B streptogramins, which are polyunsaturated macrolactones and cyclic hexadepsipeptides respectively.

Group A and Group B streptogramins, when present together, have a markedly enhanced effect on blocking bacterial protein synthesis.

[Slide.]

Streptogramins can be grouped with macrolides and lincosamides, the so-called MLS antibiotics, which are common in blocking protein synthesis at the bacterial ribosome, although their microbiologic effects differ.

An oral streptogramin, Pyostacine from RPR, has been used in France for over 30 years for treating less serious gram-positive infections.

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Anticipating a health threat from serious gram-positive infections, research and development of Synercid was begun in the early 1980s.

[Slide.]

Streptomyces pristinaespiralis produces pristinamycin IA, which is a Group B streptogramin, and pristinamycin IIA, which is a Group A streptogramin. These are solubilized to produce quinupristin and dalfopristin in a natural 30 to 70 percent ratio. Further processing yields Synercid as a freeze-dried product.

[Slide.]

Derived from natural fermentation products, both quinupristin and dalfopristin are composed of a number of closely related compounds with similar microbiologic activity. On this slide, the major components are shown. The 30 to 70 percent ratio produces a potent synergistic antibacterial effect.

[Slide.]

The important microorganisms susceptible to Synercid include primarily gram-positive organisms, both susceptible and resistant strains of *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Streptococcus pneumoniae*, and *Enterococcus faecium*. There is some activity against gram-negative and the atypical bacteria.

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[Slide.]

Based on the microbiologic profile of Synercid, RPR conducted clinical trials, designed in conjunction with FDA, and according to FDA's Points to Consider and IDSA guidelines, for the treatment of: nosocomial pneumonia, complicated skin and skin structure infections, community-acquired pneumonia.

These were comparative trials utilizing the rigorous active controls shown. The number of trials for approval is based on FDA's Points to Consider and include one study for nosocomial pneumonia and two studies for community-acquired pneumonia.

For complicated skin and skin structure infections, RPR agreed with FDA to conduct an additional study, that is, two studies, one more than required in the FDA's Points to Consider.

The effectiveness of Synercid in treating serious gram-positive infections, including VREF and staphylococci, were evaluated in four non-comparative trials through an emergency use program, which to date has treated approximately 3,000 patients.

[Slide.]

Analysis of the clinical trial data has demonstrated Synercid's effectiveness with acceptable

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safety. In September of last year, RPR submitted NDAs seeking FDA's approval for the following indications and for the primary pathogens shown:

Infections due to vancomycin-resistant *Enterococcus faecium*; infections caused by *Staphylococcus aureus* in patients failing other therapies; nosocomial pneumonia; complicated skin and skin structure infections; and community-acquired pneumonia caused by culture-proven monomicrobial *Streptococcus pneumoniae*.

All indications include cases of concurrent bacteremia and for *Staphylococcus aureus* includes MRSA.

Following the presentations today, RPR will be glad to answer any questions.

[Slide.]

Dr. Michael Edmond will now address the epidemiology of serious gram-positive infections.

Epidemiology of Serious Gram-Positive Infections

DR. EDMOND: Good morning.

[Slide.]

Antibiotic-resistant gram-positive organisms have played an important role in American hospitals for the last 50 years. In the 1950s through the 1970s, penicillin-resistant staphylococci were very problematic, and in the 1960s through 1980s, methicillin-resistant Staph

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aureus became common.

Currently, the gram-positive organisms that we deal with in our hospitals include vancomycin-resistant enterococcus, penicillin-resistant pneumococci, and within the last two years we have had descriptions of glycopeptide intermediate Staph aureus. In the future, we are concerned that we may see fully resistant Staph aureus isolates to vancomycin.

[Slide.]

The gram-positive organisms are clearly important. If you look at these data from the SCOPE project, from 1995 and 1996, looking at nosocomial bloodstream infections of around 5,000, you see that the gram-positive organisms account for nearly two-thirds of all these nosocomial bacteremias, and when you review the rank order of pathogens, you see that the first three are all gram-positive: the coagulase-negative Staphylococci followed by Staph aureus, and then Enterococcus.

[Slide.]

Vancomycin resistance in the gram-positive organisms can be divided into those organisms which are innately resistant to vancomycin or have intrinsic resistance. These tend to be not as clinically important and not as epidemiologically important and those in which

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vancomycin resistance has been acquired, and as you can see here, quite a long list including importantly Enterococcus faecium and faecalis, and also Staphylococci, initially the coagulase-negative and more recently Staph aureus.

[Slide.]

As Dr. Murray mentioned to you, the enterococci are very important nosocomial pathogens for a number of reasons. They are normal flora in the GI tract, which makes them ubiquitous, they are inherently at least relatively antimicrobial resistant even in their most naive state, and that allows them to survive in an environment with heavy use of antibiotics, which is the hospital.

They are hardy organisms. They can survive heat and desiccation. They can live in the environment for prolonged periods of time.

Lastly, health care workers provide the potential for spread of these organisms primarily through non-compliance with hand-washing.

[Slide.]

In this timeline, you can see how enterococci have acquired resistance over the last 30 years. In 1970, the first cases of high level streptomycin resistance were reported. Almost 10 years later, the first cases of high level gentamicin resistance. In the early 1980s, Dr. Murray

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reported the first cases of beta-lactamase production, in the mid-1980s, the resistance to glycopeptides, and by 1991, cases were being reported of infections due to enterococci which were resistant to essentially all available antibiotic agents.

[Slide.]

These are newer data which look at vancomycin resistance in nosocomial enterococcal bloodstream infections from about 50 hospitals across the United States. You can see in 1995, the overall rate of vancomycin resistance in these infections was about 13 percent. However, when you look at it by species basis, you see that *E. faecium* is much more problematic here.

Approximately 40 percent were resistant to vancomycin. One year later that number was more than 50 percent with an overall rate of 16 percent resistance to vancomycin.

[Slide.]

Enterococcus is an important organism because of the outcome. Many studies have looked at crude mortality of enterococcal bacteremia. Those studies are very difficult to interpret because these patients often have many comorbidities, but you can see that in the vancomycin susceptible area, crude mortality rates of 34 to 46 percent

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were reported, and with vancomycin-resistant infections, anywhere from 17 to 100 percent mortalities have been reported.

The attributable mortality has been determined using a model, similar for both vancomycin-susceptible enterococcal bacteremia and vancomycin-resistant. For vancomycin-susceptible bacteremia it has been determined to be, in this study 31 percent, and for vancomycin-resistant enterococcal bacteremia 37 percent.

[Slide.]

The coagulase-negative staphylococci are also very important. They continue to be the leading cause of nosocomial infections in the United States. They are commonly a cause of prosthetic device infection and often that device will need to be removed.

Somewhere between 60 and 90 percent of strains of coagulase-negative staph are methicillin resistant, and the first reports of vancomycin resistance in *Staph haemolyticus* were reported in 1987.

[Slide.]

For *Staph aureus*, the timeline here shows that the first cases of penicillin-resistant *Staph aureus* were reported in 1948, just a few years after the introduction of penicillin. In 1961, the first cases of

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methicillin-resistant Staph aureus were reported, just one year after the introduction of the clinical use of methicillin.

In 1975, the first cases of MRSA, which were multidrug-resistant, later determined to be of the MLS-VC type. By 1996, the first case of vancomycin intermediate Staph aureus was reported from Japan.

[Slide.]

Methicillin-resistant Staph aureus also continues to be a major hospital and community pathogen. In the hospital, it is most frequently spread from patient to patient via the hands of health care workers.

Up to 1 percent of patients who were admitted to hospitals where this organism is endemic may become colonized, and once colonized, 30 to 60 percent will go on to develop infection.

In the graph on the right, you see the percent of Staph aureus isolates reported as methicillin resistant from various surveys. In the United States, in 1975, from CDC, reporting that only 2 percent of Staph aureus were methicillin resistant, and in 1996, about 35 percent resistant.

A study from Japan in the early 1990s showed that 60 percent of Staph aureus isolates were methicillin

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resistant.

[Slide.]

More recently, we have seen the problem of glycopeptide-intermediate Staph aureus. The index case was a 4-month-old boy in Japan who developed sternal wound infection with a methicillin-resistant Staph aureus strain that had a vancomycin MIC of 8 mcg/ml.

The mechanism of resistance here remains unknown, although it has been shown not to be van A or van B. It is thought to be due to enhanced cell wall synthesis.

Another strain discovered in Japan, the Mu3 strain, contains vancomycin-resistant subpopulations or so-called hetero-resistant Staph aureus, which in the presence of vancomycin can produce subclones with MICs of 8.

Screening of more than 1,000 clinical MRSA isolates from 203 Japanese hospitals has revealed so-called heterotypic-resistant rates of 20 percent in this index hospital, 9 percent in the 7 university hospitals, and 1 percent in non-university hospitals.

Importantly, two cases of glycopeptide intermediate Staph aureus infections have been described in the United States in 1997. Both of those isolates had vancomycin MICs of 8 mcg/ml.

[Slide.]

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Lastly, penicillin-resistant pneumococci remain important. The first reports came from Australia in 1967, New Guinea in 1969, and then South Africa in 1977.

It is an important community-acquired pathogen; however, transmission of these resistant strains has been documented in hospitals and nursing homes, and these strains are often resistant to other antibiotics including macrolides, tetracyclines, and trimethoprim sulfamethoxazole.

The graph on the right, you can see rates of penicillin resistance from two different studies. This is a study that surveyed isolates from 1979 through 1987, more than 5,000 isolates, showing a 5 percent rate of intermediate penicillin resistance and a far less than 1 percent rate of high level penicillin resistance.

A more recent study from 1996 to 1997 done nationally with more than 9,000 isolates shows now that the rate of intermediate resistance to penicillin in the pneumococcus is 20 percent, and 14 percent of isolates are now showing high level resistance.

[Slide.]

So, in summary, the gram-positive organisms account for two-thirds of nosocomial bloodstream infections. The rates of antibiotic resistance in this organisms are

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increasing.

Although glycopeptide resistance has emerged focally, it is likely that it will spread widely similar to vancomycin-resistant enterococcus. The emergence of vancomycin resistance in the enterococcus and staphylococci, as well as penicillin resistance in pneumococcus, underscores the need for new antimicrobial agents.

Medical Need

DR. GILBERT: I am Dr. Gilbert and I would like to spend just a few minutes to further amplify the bedside impact of the remarks of both Dr. Murray and Dr. Edmond.

[Slide.]

Of course, at the bedside, efficacy is always the first choice and unfortunately, the statistics that you have heard have increasingly led to our concern about resistance especially when we have a sick patient in front of us and we don't yet have any culture results.

[Slide.]

The three organisms that we are addressing today are the gram-positive cocci. Obviously, there are parallel concerns about gram-negative organisms, as well.

[Slide.]

Ron Jones provided me with these statistics that I think parallel and support the data that have already been

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presented this morning. It is interesting that there is this dramatic increase in the incidence of vancomycin-resistant enterococci, but even a more dramatic increase in the incidence of resistance of pneumococci to penicillin. This, by the way, is one of the higher numbers I have seen. In our own local locale, it is about 30 percent with half of that being high level resistance and half intermediate resistance, but certainly these kinds of numbers impact one's thinking when it comes to empiric choice of therapy.

The methicillin-resistant staph problem, as Mike just mentioned, continues to increase.

[Slide.]

Now, what options are available? This summarizes the remarks of Dr. Murray and extends them to the resistant pneumococcus. If we suspect or have evidence of resistant Staph aureus or Staph epidermidis, vancomycin is our only choice at the present time.

It has become apparent in recent years that even though it is our only choice, it is only slowly bactericidal and many clinicians will add rifampin. For the penicillin-resistant pneumococcus, vancomycin, as mentioned, is frequently chosen.

It is interesting that it is not a licensed

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indication, there have never been any comparative studies, but it apparently is the drug that we often turn to, so for both MRSA, MRSE, penicillin-resistant pneumococcus, we are put in this position of looking to vancomycin for empiric or specific therapy even though we, on the other hand, would like to avoid the use of vancomycin, so as to lessen the pressure on selection of resistant enterococci and other organisms.

Ceftriaxone is currently the standard for community-acquired pneumonia. There is cross resistance among the pneumococci. If it is high level resistant to penicillin, about half of those strains will also have resistance to ceftriaxone.

I have surveyed some of my colleagues if they have seen any failures of the use of ceftriaxone in the treatment of community-acquired pneumonia. To my knowledge, that has not yet been documented, but one worries that it is just around the corner, because there certainly have been failures of the treatment of ceftriaxone in the treatment of meningitis due to resistant pneumococci.

There are selected fluoroquinolones that have activity against the resistant pneumococcus. Thus far, the numbers are small. The fluoroquinolones certainly look attractive in this regard, but the fluoroquinolones have

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shown this propensity for rapid development of resistance, so close monitoring of that utilization of fluoroquinolones is certainly going to be of interest.

I hardly could amplify further on Dr. Murray's discussion of the alternative drugs for vancomycin-resistant *S. faecium*. Just a couple of editorial comments, if you will.

It is my understanding that novobiocin production has ceased in this country. That drug showed static activity and was often used in combinations, as stated earlier, but now I don't even think it is available.

Teicoplanin is not available in the U.S., and then the other drugs that Barbara mentioned.

[Slide.]

In short, clearly, this resistance problem is having an impact at the bedside against clinical decisionmaking and the use of antimicrobials when there are proven or suspected infections due to MRSA--should also say MRSE--penicillin-resistant pneumococci or resistant enterococci.

[Slide.]

Lastly, I couldn't resist a brief editorial comment of the difficulties in trying to show the efficacy and safety with such resistant gram-positive cocci. It was

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only 10 or 15 years ago when it was customary, when evaluating the new antibacterial for various infections of the organ systems listed that one could easily select out a comparison-approved drug that was active against the microorganisms that would cause skin and soft tissue infections, community-acquired pneumonia, and so forth, and then the new drug would undergo clinical trials and have to show comparative or better efficacy than the standard drug.

Ten or 15 years ago, we didn't have any antivirals. The first drugs for HIV, herpes simplex, and so forth, had to be tested for their safety and efficacy without a comparative randomized trial. Well, now we have new antivirals that we can do comparative randomized trials and we are talking about a resistant organism for which there is no comparative drug.

Thank you.

Microbiology Profile

DR. NADLER: Good morning. I am Harriette Nadler. I will share with you some highlights of the microbiological profile of Synercid.

[Slide.]

I will begin with the synergistic mode of action at the ribosome. I will continue with the spectrum and potency of activity. I will characterize and describe the

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impact of macrolide and lincosamide resistance, and contrast that with the streptogramin-specific resistance mechanisms. Then, I will finish with the potential for resistance development to Synercid.

[Slide.]

Synercid acts at the bacterial ribosome by inhibiting protein synthesis. Streptogramin A, or dalfopristin, blocks an early step of protein synthesis elongation. Also, dalfopristin causes a conformational change in the ribosome which actually increases the affinity for streptogramin B, or quinupristin.

Quinupristin blocks a later step of protein synthesis peptide bond formation. This leads to a release of incomplete peptide chains. The combination of the two, streptogramin A and B, results in synergy and a dual metabolic block which leads to irreversible damage to the bacteria.

[Slide.]

Unlike macrolides and lincosamides, Synercid is synergistic and bactericidal. It is composed of two components, quinupristin and dalfopristin, in a 30 to 70 weight by weight ratio.

Synercid, however, acts like one drug because the combination is effective in the mouse thigh model and also

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in vitro over a wide range of ratios. Those that include 3 to 1, and 1 to 1 of quinupristin and dalfopristin that occur after administration to man. Synercid is up to 16-fold more active than either component tested individually.

The metabolites of quinupristin and dalfopristin also contribute to the antimicrobial activity and to the synergy.

[Slide.]

The synergistic activity has been demonstrated with a variety of gram-positive pathogens. Using the largest in-vitro susceptibility database, we see the MIC 50 and 90 values were all less than or equal to 1 mcg/ml with no difference observed between the methicillin-resistant and methicillin-susceptible counterparts. Please note that 1 mcg/ml or less is considered the proposed susceptible breakpoints. Also, note that Synercid is not active against *E. faecalis*.

Although not in the dossier, we have received information subsequent to the filing from Dr. Tenover of the CDC. He reports that there have been 12 methicillin-resistant staphylococcus species with intermediate resistance to glycopeptides, and all of them have shown in-vitro susceptibility to Synercid.

[Slide.]

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The synergistic activity is also seen with streptococci. The MIC 50 and 90 values were all less than or equal to 1 mcg/ml with minimal difference seen between the penicillin-resistant and susceptible counterparts.

[Slide.]

In addition to the synergistic activity, Synercid shows a post-antibiotic effect. The in vivo post-antibiotic effect is defined as the difference in time between drug treated and untreated tissues or fluids to show 1 log of growth after the serum levels falls below the MIC.

For Synercid, this was an unusually long period of time. You see here 10 hours with the methicillin-susceptible Staph aureus. This compares to values of 4 to 6 hours found in vitro for erythromycin-resistant Staph aureus, and those values were obtained with 50 percent lower drug concentrations than those used in this in vivo model.

The presence of a post-antibiotic effect that is so prolonged may help explain efficacy observed for periods that are longer than those we would predict based on the half-life of Synercid.

[Slide.]

Macrolides, lincosamides, and Synercid inhibit bacterial protein synthesis, and bacteria can resist this

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action, but this impact differs across these drugs. The resistance can be constitutive, that is, present unconditionally, impacting all drug types or present only when induced, that is, by the 14 and 15 carbon macrolides.

Synercid, due to the presence of streptogramin A or dalbapristin retains synergy in activity.

[Slide.]

Synercid's anti-staphylococcal activity is retained despite the presence of various MLS-resistance mechanisms we see depicted here. Please note most of these mechanisms are uncommon. The common mechanism is the MLSBC constitutive phenotype. In our global database we see this in 80 percent of the MRSA. Hence, MRSA are considered cross-resistant to the MLS drugs.

[Slide.]

A global view of all in vitro and in vivo studies that have been conducted indicate that the MLSB resistance did not consistently impact bactericidal activity of MRSA. Some studies have reported diminished killing for some of the strains, but our knowledge of this impact has changed with time.

More drug was required to treat MRSA versus MSSA in the mouse model, however, the dosing and pharmacokinetics in the early endocarditis models did not closely simulate

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that of man. Furthermore, low drug concentrations and uncharacterized strains in the early in vitro studies may have contributed to the inconsistency of bactericidal activity reported.

Your briefing document shows preliminary data from the rat endocarditis model that now has optimal dosing, and it does indicate that Synercid is at least as bactericidal as vancomycin.

In addition, the MLSB-inducible resistance does not have an impact on Synercid's activity. If erythromycin-inducible resistant strains were exposed to Synercid, cross resistance to lincosamides and quinupristin did not develop.

[Slide.]

Synercid is bactericidal against multiresistant staphylococci. We can see a 3-log decrease in the CFU at low multiples of the MIC within several hours. Please note there is also little difference in the killing effect across the concentrations.

Data in your briefing package shows that staphylococci are also killed within macrophages.

[Slide.]

Here are the mechanisms which do impact Synercid activity, however, the resistance to Synercid remains low,

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that is, 2.7 percent in a country which has used oral streptogramins for at least 30 years.

In contrast, a recent North American survey conducted after our dossier was filed shows less than 1 percent resistance to Synercid, and that is of course before widespread use.

Further, resistance to Synercid requires the presence of multiple mutations that target both the quinupristin and dalfopristin components. I would add that multiple mutations were seen with a single instance of MRSA emerging resistance from the clinical program.

[Slide.]

MLSB resistance did not impact inhibitory activity for any of the multiresistant pathogens. What we did see is that the bactericidal activity for E. faecium was impacted, and E. faecium generally, VREFaecium possesses the MLS resistance.

There was a rabbit model with E. faecium causing endocarditis. Although the rabbit model was an early one and wasn't optimally dosed, the low degree of killing that was observed has been confirmed with a number of in vitro studies.

According to the data in your briefing document, as I just mentioned, bactericidal activity versus MLSB-C,

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MRSA was recently achieved in the rat endocarditis model. Pneumococci with the MLS resistance are killed quickly in vitro starting at 10 minutes with corresponding efficacy in a mouse pneumonia model.

[Slide.]

Although the mechanisms which are known to impact Synercid's activity are expected to be uncommon, it is important to discuss the three basic elements involved in determining the potential for resistance development - the pathogens, the drug attributes themselves, and of course the treated human host.

[Slide.]

Synercid does retain activity against the vast majority of strains tested. In the recent resistant trend survey conducted after the filing to the FDA, we see that Synercid remains susceptible to at least 98 percent of beta-lactam or glycopeptide resistant strains.

This study represents optimized techniques for bacterial identification of enterococci and also optimized techniques for in vitro susceptibility testing. The former are particularly challenging for the clinical laboratory.

[Slide.]

Synercid is excreted largely in the bile. Consequently, in healthy volunteers, we did see a several

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log increase in the CFU of enterococci. This was comprised largely of *E. faecalis* and to some extent we did see increases in *E. faecium* after five days of treatment.

This effect showed a trend to return to normal one month later. If we look to the VRE*Faecium*-infected patients, the bile burden of VREF is reduced several logs following treatment with Synercid.

[Slide.]

A low incidence of resistance is predicted based upon Synercid's attributes. The streptogramins represent a novel drug class for the United States and cross resistance with other drug classes is not expected. The dual mode of action leads to the requirement for multiple mutations before resistance to Synercid develops and we also have seen the mutation frequency rates in vitro were rare.

Synercid has a focused spectrum of activity and is not expected to impact the gram-negative flora. Synercid may be safely combined with other antibacterial agents.

[Slide.]

In summary, as shown in numerous global studies, Synercid represents a novel drug class, retaining activity in vitro and in vivo against most gram-positive strains resistant to other drug classes.

In vitro activity against glycopeptide

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intermediate staphylococci was also noted in contrast to macrolides and lincosamides, bactericidal activity and long post-antibiotic effects were commonly seen with streptococci and staphylococci.

Post-antibiotic effects and generally bacteriostatic activity was seen with VREFaecium.

In addition, based on the data at hand, a slow resistance development to Synercid is predicted based on the requirement for multiple mutations.

I thank you for your attention. I would like to introduce to you the next speaker, Dr. Jerry Rhodes of the Drug Metabolism and Pharmacokinetics Group.

Clinical Pharmacology

DR. RHODES: Good morning.

[Slide.]

I would like to provide an overview of the clinical pharmacology of Synercid. As described by Dr. Nadler, Synercid is an antibiotic agent whose activity derives from the synergistic activity of the two streptogramin components quinupristin and dalfopristin.

Consequently, a description of the in vivo profile of Synercid is important in moving from the in vitro microbiology data conducted at a fixed 30 to 70 ratio of quinupristin to dalfopristin to an understanding of the in

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vivo activity of Synercid.

To describe the in vivo disposition profile of Synercid, I will summarize the most pertinent data from pharmacokinetic studies conducted in human volunteers and in infected patients. This data was obtained using sensitive HPLC methods and two selective bioassays which measured quinupristin and dalfopristin related activity respectively.

I will also summarize the pharmacokinetic/pharmacodynamic relationships underlying antibiotic activity. Due to the potent synergistic activity of quinupristin and dalfopristin, I want to emphasize that I will be describing the PK/PD of Synercid and pharmacokinetic parameters thought to be most predictive of activity in vivo.

[Slide.]

Let's move to a description of the in vivo profile of Synercid. This graphs shows the plasma concentration time profile of quinupristin and dalfopristin at the dosage of Synercid administered in clinical trials.

Dalfopristin plasma concentrations are higher than those of quinupristin and peak at approximately 7 mcg/ml. Quinupristin peak plasma levels are approximately 3 mcg/ml.

[Slide.]

As can be observed, the plasma profiles of

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dalfopristin and quinupristin are qualitatively similar, the difference in magnitude during the infusion period being roughly equivalent to the dosing ratio.

Although the dalfopristin concentrations fall more rapidly post-infusion, it is important to note that over the portion of the plasma concentration profile that carries the majority of the area under the curve, the quinupristin to dalfopristin ratio varies over a relatively narrow range.

[Slide.]

That is shown here. A mean quinupristin-dalfopristin ratio is observed in vivo range from approximately 0.25 at early timepoints to approximately 1.4 at later timepoints. These are within the range of ratios as shown by the two dotted lines on the graph at which synergistic activity has been demonstrated.

[Slide.]

A similar profile observed in vivo arises because the pharmacokinetics of quinupristin and dalfopristin are comparable. The systemic clearance of quinupristin and dalfopristin are high. They approximate liver blood flow in human subjects and are similar.

The half-lives of quinupristin and dalfopristin are both less than an hour, but as I will describe in a moment, half-life was not a critical parameter in describing

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PK/PD relationships for Synercid.

The steady-state volumes of distribution of quinupristin and dalfofristin are moderate, a slightly higher volume being observed for quinupristin. It is also important to note that the pharmacokinetics of quinupristin and dalfofristin are linear over the therapeutic dosage range.

[Slide.]

The distribution volume of quinupristin and dalfofristin is consistent with tissue penetration. The plasma protein binding is low, approximately 55 percent for quinupristin and 26 percent for dalfofristin. Thus, the free fraction of drugs circulating in plasma and available for diffusion to infected sites is high, and changes in the free fraction of drug to disease states of protein binding interactions would be unlikely.

Synercid has been shown to diffuse into non-inflammatory blister fluid in normal human volunteers. The area under the blister fluid curve was approximately 40 percent that of the plasma AUC. The blister fluid concentrations observed were above the MIC's susceptible strains, and approximately 2-fold longer half-life was observed in blister fluid.

Synercid diffusion into human PMNs was also

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studied in healthy volunteers. Both quinupristin and dalfopristin showed significant penetration in vivo into human leukocytes.

[Slide.]

That distribution is shown here. The concentrations of quinupristin and dalfopristin in human leukocytes is significantly higher than that observed in plasma, resulting in significant PMN-to-plasma ratios for both Cmax and AUC.

It is also clear from these curves that significant concentrations of quinupristin and dalfopristin are present in circulating leukocytes at times as late as 8 hours following administration with Synercid after plasma concentrations have fallen significantly.

Ex vivo studies in human macrophages have also shown that Synercid is active against intracellular Staph aureus.

[Slide.]

Following administration of Synercid in human subjects, both quinupristin and dalfopristin are mainly cleared via metabolism. Quinupristin is metabolized mainly into two major metabolites, glutathione and a cysteine conjugate. Dalfopristin is mainly metabolized into pristinamycin IIA, which is then further metabolized via

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conjugation and other routes of metabolism.

These three major metabolites and other minor metabolites are cleared primarily via biliary excretion.

As mentioned previously, the glutathione and cysteine conjugates of quinupristin and pristinamycin IIA have been shown to be microbiologically active in vitro and to possess synergistic activity with a corresponding parent drug. In addition, these metabolites have been demonstrated to circulate in human plasma, and I will come back to their in vivo significance in a moment.

It is important to note at this point, however, that the major biotransformation routes for Synercid, for both quinupristin and dalfopristin are not mediated by cytochrome p450 isozymes and consequently, the pharmacokinetic profile of Synercid will not be altered significantly via cytochrome p450 interactions with other co-administered drugs.

[Slide.]

Although quinupristin and dalfopristin are not significant substrates for cytochrome p450 isozymes, both components inhibit cytochrome p450 3A4. This inhibition has been demonstrated in vitro at concentrations similar to those found in vivo for both quinupristin and dalfopristin for several model 3A4 substrates including cyclosporine,

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nifedipine, and midazolam.

Inhibition was also confirmed in vivo in a drug interaction study in which Synercid increased the systemic exposure of cyclosporine as evidenced by a 63 percent increase in cyclosporine AUC.

Positively, quinupristin and dalfopristin have no significant effect on other p450 isozymes. However, Synercid does have the potential to cause drug interactions by increasing the plasma concentrations of other co-administered CYP 3A4 substrates.

[Slide.]

In comparing the pharmacokinetics of Synercid in young healthy male volunteers to other subject populations, no significant differences in kinetics have been observed with gender or with age. In addition, no significant pharmacokinetic differences were observed in patients with severe renal insufficiency.

[Slide.]

Consequently, a positive feature of Synercid is that no dosage adjustment may be necessary for infected patients with renal insufficiency. However, there were significant changes in the pharmacokinetics with Synercid in subjects with hepatic insufficiency classified by Child-Pugh score.

ajh

Although systemic levels of quinupristin and dalfopristin were comparable in these subjects, the glutathione and cysteine conjugates of quinupristin and pristinamycin IIA increased by approximately 2.8- and 1.5-fold respectively.

This is a result that would be expected since these metabolites are primarily excreted in the bile. Thus, in patients with hepatic insufficiency, a dosage reduction to 5 mg/kg is recommended if the tolerability of Synercid is not acceptable.

[Slide.]

So, what is the in vivo significance of the metabolites of Synercid? We compare the steady-state pharmacokinetic profiles of quinupristin, dalfopristin, and their major metabolites are shown here.

Based on Cmax and AUC values for the parent drugs, it is clear that quinupristin and dalfopristin are the major active circulating components in plasma. The metabolites of quinupristin and dalfopristin, however, do have longer half-lives than the parent drug and thus are eliminated more slowly.

From the AUC values of the metabolites, it is clear that the metabolites of Synercid contribute to the in vivo antibiotic activity of this drug. Consequently,

ajh

Synercid presents an interesting picture in relating its pharmacokinetic and pharmacodynamic characteristics.

[Slide.]

So, let's turn now to Synercid pharmacokinetic/pharmacodynamic relationships. From studies conducted in preclinical models of infection, it is clear that Synercid has in vivo bactericidal activity. Following administration of Synercid, a prolonged post-antibiotic effect of 9 to 10 hours has been demonstrated in a mouse thigh infection model with Staph aureus and Strep pneumonia.

In addition, two preclinical animal models of infection, a mouse thigh infection model with Staph aureus and Strep pneumonia and a rabbit endocarditis model with methicillin-resistant Staph aureus have shown that the pharmacokinetic parameter most predictive of in vivo efficacy was the AUC-to-MIC ratio.

Time above the MIC was not a pharmacokinetic parameter that was predictive of in vivo efficacy in these models.

[Slide.]

Other factors need to be considered in describing the pharmacokinetic/pharmacodynamic relationships of Synercid. Quinupristin and dalfopristin individually show weak bacteriostatic activity, however, they demonstrate a

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16-fold more potent bactericidal activity for most gram-positive pathogens in combination as Synercid.

This has been demonstrated in vitro and in vivo in preclinical animal models. This potent synergistic activity exists over a wide ratio of quinupristin-to-dalfopristin concentrations. Consequently, the PK/PD relationships of Synercid, and not individually quinupristin or dalfopristin, is the most relevant in describing the in vivo activity observed.

Thus, our approach to describing the PK/PD of this novel antibiotic has been to combine the plasma concentrations of quinupristin, dalfopristin, and their active metabolites, and to express their summation as an approximation of the pharmacokinetic profile of Synercid.

[Slide.]

That treatment is shown here for human subjects where plasma concentrations of Synercid, the sum of quinupristin- and dalfopristin-related activity plotted versus time. The reference MIC value of mcg/ml, shown here, would be effective against 98 percent of the strains for Synercid's targeted pathogens.

From this analysis, it is clear that significant concentrations of Synercid are achieved above this MIC level, and that the majority of the area of the curve

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resides above this reference MIC value.

[Slide.]

In conclusion, the pharmacokinetic relationships with Synercid supported a q8 or q12 hour dosing regimen, and taken together, the pharmacokinetics/pharmacodynamic characteristics of Synercid, provide an appropriate in vivo profile for this novel antibiotic.

I would now like to turn the presentation over to Dr. George Talbot who will describe the clinical trial data for Synercid.

Clinical Trial Data

DR. TALBOT: Thank you. Mr. Chairman, members of the committee, invited guests, ladies and gentlemen.

[Slide.]

My name is George Talbot. I am very pleased to present to you today the results of the clinical trials program for Synercid.

[Slide.]

The points I will address in my presentation today are shown in this first slide. I will first discuss the clinical development of Synercid beginning with the rationale for its development. I will review efficacy data from emergency-use studies, efficacy data from the comparative studies, what we term integrated efficacy data

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as well as integrated safety data.

I will then present our conclusions about the potential role of Synercid in the therapeutic armamentarium.

[Slide.]

The rationale for the clinical development of Synercid is shown in this slide. There are two major reasons. First, of course, is the anticipated medical need for the product. This need has been amply described by Dr. Murray, Dr. Edmond and Dr. Gilbert. This need, in fact, was apparent in Europe in the late 1980s because of the emergence of *Streptococcus pneumoniae* with decreased susceptibility of penicillin.

The second major reason for the development of this compound was its in vitro spectrum of activity versus multiresistant gram-positive organisms as described by Dr. Nadler. First of all, of course, *Staphylococcus aureus* but also coagulase-negative *Staphylococci*, *Enterococcus faecium*, *Streptococci* including *S. pneumoniae* and also intracellular pathogens.

[Slide.]

Clinical development of Synercid was focused on a specific target population; that is, hospitalized patients with moderate to severe infections plus pathogens lying within spectrum of activity of this drug.

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The initial development strategy, shown here as the second bullet, focused on what I call traditional indications; that is nosocomial pneumonia, complicated skin and skin-structure infection, and community-acquired pneumonia.

However, this strategy was revised in 1994 in conjunction with our colleagues at FDA as well as those in the clinic due to the increasing prevalence of infection caused by VREFaecium, or VREF.

Soon thereafter, the development strategy was further extended to include other multiresistant gram-positive infections including specifically those in patients failing, or intolerant of, standard therapies.

[Slide.]

The phase II and phase III develop program is highlighted or overviewed on this slide. I have shown you the treated population, the number of patients who received Synercid, the dose and dose interval of Synercid and the maximum per-protocol treatment duration.

There were four phase II studies, two pilot studies in which a total of 24 Synercid patients were treated at the dose range indicated. These were followed by comparative studies in which a total of 130 patients

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received Synercid. These were comparative studies as well so there were, in addition, comparative treated patients.

Based on the preclinical data and the results of these phase III studies, the decision was made to enter phase III with a dose of 7.5 mg/kg given every eight or every 12 hours.

I have shown here first the emergency use studies. There were four of them, and, in the NDA, we are presenting data on almost 1200 patients treated under this program.

The traditional program, as I'll call it, included two studies in community-acquired pneumonia, dose 7.5 q12, two studies in complicated skin and skin-structure infection with the same dosage regimen, and one study per FDA guidelines in nosocomial pneumonia at 7.5 mg/kg every eight hours.

The total number of Synercid-treated patients in phase III was 2,298.

[Slide.]

Let me speak first about the emergency-use studies. There were a number of substantial design considerations in this program. First of all, I have to say that there was a substantial scientific challenge. I think Dr. Murray has already alluded to some of the issues that we faced in designing and executing this program.

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Specifically, we had to assess efficacy and safety in patients with resistant pathogens and in those who failed or were intolerant of available treatments. Because of the challenges we faced, we defined inclusion and exclusion criteria, the infection sites to be studied, the study endpoints and key efficacy and safety parameters with FDA.

We required that patients have bacteriologically documented infection at entry. We utilized a central laboratory. Dr. Robert Moellering in Boston kindly offered his services to us. He performed both pathogen identification and susceptibility testing on isolates sent from the local site laboratories.

Finally, we spent considerable time defining our data analysis plan, discussing options and approaches. This plan was validated with external experts including Dr. Moellering as well as Dr. David Gilbert and Dr. Peter Linden. Dr. Moellering further reviewed the statistical analysis plan.

[Slide.]

There were some other design considerations. The first of these was whether or not a comparator arm could have been included in these studies. This was discussed early on with FDA and it was concluded at the time these studies began in 1993 that an adequate control group was not

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possible.

First of all, there was no FDA-approved antibiotic or antibiotic combination for the treatment of infections due to VREF. Furthermore, as Dr. Murray, Dr. Edmond and Dr. Gilbert have highlighted, there really was no standard of care in practice.

It was considered whether a placebo control group could be utilized. This was judged neither ethical nor, in fact, practical. It must be said, at the time the program was being discussed with FDA, that we had in hand, and they were aware of also, the fact that there were encouraging results already available from the first patients treated for VREF in this program.

[Slide.]

This slide shows the four phase III emergency studies which were included in our NDA. We show you features of the design, pathogens treated, dose regimens and assessments.

Study 399 refers to the retrospective collection of data from the very first patients enrolled in these studies. This study is followed by study 398 and 301. 398 is further subdivided in 398A and 398B, where 398B simply a continuation in time of study 398A.

Study 398 and 301 were prospective. Studies 399

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and 398A and 398B allowed patients with any gram-positive pathogen and specifically focussed on those that had previous treatment failure, had antibiotic tolerance or were judged to have alternative therapy.

In contrast, study 301 focused on VREF only. A dose of 7.5 mg/kg was used in each of these studies. Initially, a q12 hour regimen was a possibility, but, for the later studies, q8 hours was recommended.

The first group of patients, study 399, had only end-of treatment assessment. I will remind you that this is a retrospective collection of data. In contrast, study 398A, 398B and 301 had off-treatment assessments. Because of these differences, we considered that in fact, patients in 399 were, if you will, per protocol not evaluable.

[Slide.]

Now, an additional issue we had to define disease both at the time that patients were being enrolled in this program as well as during the process of evaluability. We utilized ISDA guidelines to define indication; for example, skin and skin-structure infection.

I should point out that a patient enrolled could have only one indication, for example, skin and skin structure infection plus bone and joint infection or even skin plus UTI.

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Patients had to be culture-positive for inclusion. We carried this through into our definitions of evaluability in that the clinically evaluable population, in contrast to what you might expect to see, actually includes patients who had a pathogen.

Furthermore, for example, for the bacteremia of unknown origin indication, we required, for evaluability, that two or more positive blood cultures be obtained within seven days of entry and that, on review of the data, patient by patient, there was no apparent reversion to negative before Synercid was started.

These patients at the time of enrollment were judged to have no other appropriate therapy, specifically they had failed often or were intolerant of other therapies.

Finally, I want to emphasize that, in our enrollment, there was no exclusion for underlying diseases. This is very different from the traditional studies which you might be used to seeing where there are often a number of exclusions.

We took all comers. This was, in effect, a compassionate-use program. So a patient would not have been precluded from enrollment even if the calling physician told us that a patient had multi-organ failure and was on a downhill course.

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[Slide.]

We also defined patient response. Some of these terms are familiar to you, I'm sure. I want to focus on a couple of particular points here. We used clinical response, cure, improved or failed. We had the investigator determine this at a test-of-cure assessment. We felt the investigator was the best person to make this assessment simply because of the complexity of the patients, that the bedside judgment of whether the patient was cured, improved, failed or, perhaps, even indeterminate was best made by the investigator.

We assessed the by-pathogen response for each indication for each patient by a line-by-line review of culture results examining what results were available at the test-of-cure visit. We then constituted a by-patient response which really a programmatic compilation of the responses of each patient across all indications.

So, for example, if a patient had eradication of VREF from the urine, and had persistence at the skin site, the patient would have been a by-patient bacteriologic failure.

Finally, the overall response was compiled consisting of the combination of both the clinical and bacteriologic responses. This is, in many senses, the most

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conservative approach because, to be a success, a patient had to be both a clinical and a bacteriologic success.

We felt the clinical benefit could be determined from these parameters. We specifically discussed with our external experts whether mortality should be considered as an endpoint and we concluded that it was, in fact, an inappropriate endpoint because of multiple confounding comorbidities in this patient population.

[Slide.]

In defining evaluable populations, we did define a clinically evaluable population. I have already highlighted that this required bacteriologically documented infection, clinical response, had to be cure, improved or failure. We required at least five days of Synercid treatment for the patient to be clinically evaluable.

Let me comment on that a moment. We considered whether three days would have been appropriate but we chose five days. Five days was actually chosen by Norris et al. in the paper that Dr. Murray referred to. On reflection, we considered that, during the emergency-use program, the types of patients seen, the ones with multi-organ failure, et cetera, that we would have the best chance of ascertaining a true treatment effect if we assured that patients clearly had an adequate therapeutic trial of the drug.

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We also required evidence of treatment compliance; for example, a mean daily dose of 15 mg/kg/day or higher.

[Slide.]

Bacteriologic response for the evaluability was also defined. We further required that bacteriologic specimens be obtained within the 96 hours prior to the first dose of Synercid or up to day 2 of therapy. This was a formidable task given the fact that investigators had to call in, in many instances, to obtain drug and then we had to send the drug out to the site.

The patient could have received no presumably effective concurrent antibiotics for 20 percent or more of Synercid-dosing days. Here, we are looking specifically at chloramphenicol and doxycycline. If we knew the bug was resistant in vitro to those drugs, this was not an issue. But if we knew it was susceptible or, in fact, if we didn't know at all, we said that the patient would be excluded if, for example, during a treatment course of Synercid of 20 days, the patient received 5 days of chloramphenicol.

We applied a similar criterion to receipt of these antibiotics following the end of treatment before the test-of-cure visit.

[Slide.]

Our FDA colleagues have been very generous with us

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in sharing their briefing document and we have we met with them to discuss the results of all our studies. We appreciate that. We did, during our meeting last week, realize that there were some important methodologic differences affecting, potentially, both the evaluability and response between our methodology and the FDA's.

I present these to you just so you will be aware of the differences and not because I would propose that either approach could be inherently true or untrue, correct or incorrect. They are just different.

The clinical response determination, as I mentioned, by us was made by the investigator at the bedside. The FDA utilized the the medical officer in the determination of the clinical response. We asked our investigators to complete a patient narrative describing what happened to the patient as a supplement to a standardized case report form.

When we reviewed our cases, we reviewed the data in the CRF which we felt to be sufficient. But, whenever a narrative was available, it was reviewed and if there was any information in there which suggested that there might be an inconsistency between those data and the responses signed by the investigator, we would query the investigator to resolve the contradiction.

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In fact, this was required very, very infrequently and, in those very rare times where we did contact the investigator, it was, by far, the exception rather than the rule that there was any change to the investigator's assessment of clinical response.

I believe the medical officer, Dr. Rakowsky, will discuss their use of the patient narrative during their review of the data.

The treatment trial duration for failure I have already discussed. We use five or more days for the reasons mentioned. FDA used more than three days. For the test-of-cure window post-treatment, we used three to 21 days, the lower limit of three days being defined by the pharmacokinetic parameters of Synercid as Dr. Rhodes has described. FDA used five or more days.

There may have been other differences, but these are some of the ones of which we are aware.

With this as background, where, exactly, do we stand with the emergency-use program?

[Slide.]

This slide shows you the global emergency-use program enrollment to date. On the vertical axis, you can see the number of patients and, on the horizontal axis, the quarter. From very humble, if you will, beginnings back in

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the first quarter of '93, the rate of enrollment has increased substantially with U.S. patients being shown in blue. This takes us to the fourth quarter of '97. During that period, during this most recent period, approximately 100 to 130 patients a month were being enrolled.

There are, of course, more requests. For example, in the month of January, we enrolled 130 patients but there were approximately 188 requests. So the screening process does filter out some. And we probably received thousands of phone calls during the process.

This month, to date, a little bit more than halfway through the month, we are at a rate of about 180 patients for this month.

[Slide.]

The four studies in our program are reviewed again here, and I want to highlight the numbers of evaluable patients. In study 399, there were none for the reasons mentioned. There were substantial numbers of evaluable patients in the other studies despite the application of what we and our external experts consider to be rigorous criteria for evaluability.

My presentation will address studies with evaluable populations.

[Slide.]

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These patients were very ill, as Dr. Murray has highlighted. This slide shows you selected prognostic and risk factors at baseline by population in the emergency-use studies excluding study 399. You can see, for example, that, at entry, in the all-treated population, 57 percent of patients had one or more positive blood cultures.

I will note that almost 25 percent of patients had had transplantation and almost 20 percent of patients were on mechanical ventilation at the time of entry into the study.

[Slide.]

I will show you here the overall response rates for the emergency-use studies beginning, first of all, with the most frequent indications and for all pathogens combined; that is, not only VREF but also Staph aureus and other enterococcal species and so forth.

We focus on the most rigorously defined bacteriologically evaluable population, you can see that an overall response rate of 68 percent was defined. Looking below, you can see the results by indication. These range from 61 percent in patients with intra-abdominal infection who, very often, were liver-transplant patients, to a higher rate of 85 percent in urinary-tract infection and a gradation in between.

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[Slide.]

Let me turn briefly to the VREF subset. In the all-treated population, a response rate, an overall response rate, of 50 percent was seen. This calculation includes indeterminate responses as failures, so this is assuming that any patient labeled indeterminate was a failure.

When we turned to the evaluable populations, you can see the response rates were 69.8 percent and 65.5 percent for VREF patients across the board although we think it is better, probably, to look by indication. We are showing the overall here for convenience.

In the subset of patients who had a positive blood culture, the rates were lower, as you can see in the all-treated population, but still 55 percent in the bacteriologically evaluable population.

What about Staph aureus? We had fewer patients with Staph aureus, 65 in the all-treated population. In the evaluable population, 22 with a response rate of 81.8 percent. The most frequent indications were bone and joint, and 9 of 11 patients with bone and joint infections, had a satisfactory overall response.

[Slide.]

As a secondary analysis of the Staph data, we examined the results by resistance marker and, for the 20

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patients with MRSA, a response was seen in 18; 3 of 3 for MSSA. I will take this moment to advise you that, as mentioned previously during our presentation, that about 80 percent overall of patients with MRSA will have the MLSBC phenotype.

[Slide.]

[Slide.]

We had pediatric patients. We took all comers. There weren't very many, a total of 31 in the all-treated population and 10 and 9 in the two evaluable populations respectively with the response rates seen, 8 of in the bacteriologically evaluable group.

[Slide.]

How are we to interpret these results, this overview I have given you? First of all, clinical efficacy against VREF could be anticipated based on the in vitro microbiologic data shown to you by Dr. Nadler.

We look at evaluable populations defined rigorously on the advice of our advisors to permit assessment of the treatment effect in patients with these pathogens. Although not shown in the data, our analyses showed that efficacy was consistent across the studies and across time.

Efficacy was also consistent with what could be

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expected on an indication by indication basis, a lower rate, for example, in intra-abdominal infection, higher in urinary tract and skin.

Finally, we would like to suggest that the efficacy in these non-comparative studies should be interpreted in the context of the results from the comparative trials.

[Slide.]

Turning now to the comparative studies, these presented substantial design challenges as well. Specifically, we had to demonstrate the efficacy of a focused-spectrum antibiotic in a new therapeutic class. We felt that, in clinical practice, a drug might well be used in combination with other agents but, for the purposes of regulatory approval, in clinical trials, it was most often studied as monotherapy.

The choice of comparators was discussed with FDA, discussed extensively inside our company and with experts as well. Approved agents were used. In some instances, these represented standard-of-practice combinations, not just single agents.

Alternative treatments were allowed, as you will see in a moment. And possible on-treatment adjustments were

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allowed. None of these last three points were possible for Synercid-treated patients.

[Slide.]

Here are the phase III comparative studies, one in nosocomial pneumonia conducted in the U.S. and Europe, two in skin, two in CAP. I will note that, for each study, individually, a steering committee of external experts was constituted. One of the important roles of this committee for each study was to examine in a blinded fashion any patients for whom there were substantive questions about either evaluability or response.

[Slide.]

In nosocomial pneumonia, we conducted one statistically adequate, well-controlled study as required by FDA. The inclusion criteria, very generally, included clinically and radiographically documented pneumonia with a gram stain or other clinical data suggesting infection by gram-positive organisms.

Synercid was administered q8 hours. The comparator was vancomycin q12 with adjustments allowed for renal function and levels. Aztreonam, 2 gm q8, could be added for gram-negative bacillary coverage in both groups. Almost 300 patients were enrolled.

[Slide.]

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I am showing you the selected prognostic and risk factors at entry in the bacteriologically evaluable population. That is the primary population for efficacy as defined by the FDA. We can see that this, too, was an ill population.

For example, in the Synercid group, over 80 percent of patients were being mechanically ventilated at the time of study enrollment versus 73 percent in the vancomycin arm. If you just scan down here, you can see multilobar pneumonia, age greater than 65, bilateral disease. All were quite frequent.

In fact, 16 percent of Synercid patients and a comparable number of comparator patients, had an APACHE II score at entry above 20.

[Slide.]

The primary efficacy parameter for nosocomial pneumonia, as defined by FDA, is clinical response in the bacteriologically evaluable population. The observed rates were 56.3 percent for Synercid and 58.3 percent for vancomycin. The point estimate of the difference was minus two percentage points. The confidence interval is as shown.

These results meet FDA criteria for demonstration of equivalence.

[Slide.]

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As a secondary analysis, we looked at by-patient bacteriologic response in the same population. Rates of 58.6 percent and 64.3 percent were seen. The point estimate and confidence interval are provided for your convenience.

[Slide.]

Looking further at a by-pathogen level and examining clinical success, we focussed on the two major gram-positive infections, Staph aureus and Strep pneumoniae. In Staph aureus, the results were 27 of 52 versus 28 of 55, shown here, comparable. 8 of 20 MRSA, 8 of 18 in the vancomycin arm for MRSA as well--6 of 20 and 8 of 18 for the two treatment arms.

This can be expected in a study of nosocomial pneumonia. There were relatively fewer Strep pneumoniae and none of them were penicillin resistant. Response rates of 7 of 11 and 3 of 8 were seen.

[Slide.]

For complicated skin and skin-structure infections, two statistical adequate and well-controlled studies were performed. Patients were required to have clinical evidence of complicated skin infection presumed to be due to gram-positive organisms, at least in part. The dose regimen was Synercid q12.

There were two studies. In one study, oxacillin

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was the primary comparator. In the other, it was cefazolin. But the investigator in each study had the option to substitute vancomycin in the comparator arm as appropriate for the pathogen isolated. Aztreonam was an option for gram-positive bacillary coverage in study 305 but this was, in fact, rarely used.

Almost 900 patients were enrolled.

[Slide.]

Similarly, prognostic and risk factors present at baseline are shown here. A substantial number of patients required surgical intervention but I will highlight specifically diabetes mellitus in 28 percent of Synercid patients and some with more comparator patients and also a substantial prevalence of peripheral vascular disease.

A similar distribution of underlying factors was seen in the companion study 305.

[Slide.]

Per FDA's points to consider, the primary efficacy parameter for this indication is clinical response in a clinically evaluable population. Equivalence in demonstrated in both of these studies, 64.7 percent response rate for Synercid in study 304 versus 68.3, 71.2 and 72.5 with the confidence intervals shown.

[Slide.]

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In the secondary analysis of by-patient bacteriologic response, we saw 63 percent response rate for Synercid and 75.9 percent in study 304, the comparator. The rates were more comparable in 305. The confidence intervals are seen here for your convenience.

[Slide.]

Examining the primary pathogen concerned, Staph aureus, a rate of 64.2 percent overall for Synercid and 72.3 percent for comparator, looking in MRSA, specifically 8 of 13 versus 6 of 9.

[Slide.]

For CAP, two statistically adequate and well-controlled studies were performed. Inclusion criteria included clinical and radiographic evidence of pneumonia with the presumption that the etiologic pathogen was gram-positive. An acute 12-hour dosing regimen was used.

The comparator regimen was ceftriaxone with or without erythromycin and, as noted previously, the investigator had the option to discontinue erythromycin, continue ceftriaxone, continue ceftriaxone alone or continue both.

Over 1000 patients were enrolled.

[Slide.]

In study 302, the prognostic and risk factors at

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entry in the clinically evaluable population are shown here. Many of the criteria noted by Fine et al. in his classic article are listed here and are present in substantial numbers. I will focus on the fact that Strep pneumoniae was isolated from at least one type of specimen in one-third of Synercid patients, in about a quarter of comparator patients and about 8 percent and 7 percent--actually 8 percent and 8 percent--of patients in each group had a positive blood culture for the pneumococcus.

Similar findings were seen in a companion study.

[Slide.]

The primary efficacy parameter for this indication is clinical response in the clinically evaluable population. In study 302, the response rates were 75.5 percent and 91.2 percent. This does not meet equivalence per FDA criteria.

As you can see, a point estimate of -16.7 percent. In the lower bound, here, it is below -20. In contrast, the 303 study did demonstrate equivalence by FDA criteria with 83.1 and 87 percent response rates, respectively. For study 302, we saw parallel results for by-patient bacteriologic response.

[Slide.]

Of course, frankly, we were disappointed by the results in study 302. We did pursue an analysis of why

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there might have been a lack of equivalence in this study. We considered, for example, whether it could have had something to do with the antibacterial spectrum of the drug, the dosing interval, discontinuations due to venous intolerability in the Synercid group, choice of comparator regimen.

I think that, to sum things up, we found no clear single explanation for the discordant result versus study 303. But I do want to highlight for you that we did choose a very challenging comparator regimen in both studies.

[Slide.]

Because of the in vitro activity of Synercid against *S. pneumoniae*, we were particularly interested in looking at results in this indication for this bug. *Strep pneumoniae* was killed in the test tube within minutes by Synercid. So we examined clinical success rates in the bacteriologically evaluable population by study for patients who had *Strep pneumoniae* pneumonia, monomicrobial.

You can see that the results in this analysis are comparable, 85.7 versus 91.3 and 100 versus 100. The pooled results are seen here, 90.2 and 93.7. Confirmatory results are seen in the subset of patients who had bacteremic pneumococcal pneumonia.

Although this is a post hoc analysis, we certainly

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did not, at this point, suggest that Synercid is appropriate empiric monotherapy for CAP for an acute 12-hour regimen.

But, based on the input from our advisors who have seen this data, and given the medical need with regard to Strep pneumoniae, we think that these data are interesting and would ask that the committee consider them and their potential benefit to clinicians.

[Slide.]

How are we to interpret the results of the comparative studies? The clinical response was the primary efficacy parameter for each of these indications. In nosocomial pneumonia, in the one required study, equivalence was demonstrated. In the complicated skin and skin-structure infection studies, equivalence was demonstrated.

In CAP, equivalence to comparator is demonstrated in just one of the two studies, but efficacy was demonstrated in both; that is, the drug was certainly active in study 302 with a response rate of 75 percent.

In the post hoc analysis, we saw comparable results among microbic Strep pneumoniae infection.

[Slide.]

Let me turn, now, briefly, to some integrated efficacy data focussing on results in patients with positive

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blood cultures as well as comments about superinfection rates and emerging resistance rates.

[Slide.]

As an overview of results in bacteremic patients, specifically those identified as having one or more positive blood cultures, we see peak comparable response rates were seen. These are by-patient bacteriologic success rates. Results were also comparable in nosocomial pneumoniae in skin, although the numbers were smaller and in emergency-use program focusing just on a central-catheter-related bacteremia and bacteremia of unknown origin, we saw response rates of 74 percent.

[Slide.]

In the patient populations treated, superinfections certainly could be expected. This slide summarizes our findings. In the comparative studies, the superinfection rate of 6.8 percent was seen for Synercid as compared to 4.4 percent for comparator. These pathogens were primarily gram-negative bacilli as noted in the footnote.

The situation in the emergency-use studies with these more severely ill patients was a little bit different but the rate was not that different, although I should stress that we looked for gram-positive superinfections in

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these patients given the spectrum of activity of the drug.

In the emergency-use population, the superinfecting pathogens were primarily *E. faecalis*, as could be expected from the spectrum of activity of the drug.

[Slide.]

Emerging resistance was also sought in our database. This is defined as a four-fold or greater increase in the MIC from baseline to the isolate in question 2 or above the proposed resistance breakpoint of 4 mcg/ml. One such case occurred in the Synercid group in the comparative studies, none in the comparators. This one case was a *Staph aureus* which was MLSBC-positive at baseline but acquired insusceptible with Synercid, but acquired an additional resistance

In the emergency-use studies, there were six instances in which pairs of VREF showed emerging resistance. In one of these cases, the strain pair was not identical by molecular typing.

In two of these seven patients, emerging resistance was not associated with treatment failure. I should mention that these rates, as reported on the slide, are within the range reported in the literature and are comparable, or in some cases better than, the rates reported by Fish et al. in *Pharmacotherapy* in their extensive review

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of NDA applications.

[Slide.]

Let me turn to safety data. We analyzed non-venous events separately from venous, phase III data separately from phase I and phase II, and the comparative studies separately from emergency-use studies.

[Slide.]

When we examined, in the comparative studies, the frequency of related adverse events, we see that these were documented in 23.4 percent of Synercid patients and 20.7 percent of comparator patients. These were most common in the digestive system, body as a whole and skin and appendages system with some back and forth as to which group showed the higher frequency.

[Slide.]

Events leading to treatment discontinuation are important, of course. In the comparative studies, a rate of 6.1 percent was seen for Synercid, 2.7 percent for comparators. These related events leading to treatment discontinuation were focussed primarily on the skin and appendages system, body as a whole and digestive system with the events as noted.

[Slide.]

Turning to adverse non-venous events leading to

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treatment discontinuation in the emergency-use studies, we had to focus here because these were non-comparative studies on related adverse events. You can see that the overall rate is very comparable to that seen in the comparative studies, about 5 percent.

What we learned from the emergency-use studies was that adverse events in the musculoskeletal system were more common than in the comparative studies and also did lead to treatment discontinuation. In fact, when we look at the frequency of related arthralgias and myalgias in the emergency-use studies, we see rates of 9.5 percent and 7.3 percent, respectively.

[Slide.]

Turning to the adverse venous events in the comparative studies, 947 Synercid patients and 949 comparator patients received at least one peripheral administration of the study drug. In the comparative studies combined, the frequency of adverse venous events was 71 percent for Synercid and 45 percent for comparator.

These are not all cases of thrombophlebitis. We assessed adverse venous events assiduously and captured things such as pain, irritation, inflammation as well as overt thrombophlebitis. In CAP and skin, these rates were comparable to the rates seen overall, but in the nosocomial

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pneumonia study, the rate was lower. I would point out that in the comparator arm, including erythromycin, a fairly substantial rate of venous adverse events was seen.

[Slide.]

What about those leading to treatment discontinuation. In the comparative studies combined, 10.7 percent discontinuation rate for adverse venous events in the Synercid group, 2.2 percent for comparator. What I would draw your attention to, however, was that, in these settings, nosocomial pneumonia and emergency use, the rates were lower reflecting, perhaps, both a greater medical need and, also, the availability of administration by the central venous route.

[Slide.]

Turning to laboratory data, we conducted a thorough analysis of a large number of analytes. For your convenience, we are showing this one graphically. This is ALT, and we are showing you pre-, on- and post-treatment results for Synercid first and then comparator.

You can see, just roughly from this graph, that although there is a bump in both treatment arms, these lines are parallel and there is was no effect seen.

[Slide.]

In contrast, we did see something for conjugated

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bilirubin. We see a divergence in the curves here. The conjugated bilirubin bumps a bit in the Synercid group and comes back to baseline post-treatment whereas, for the comparator group, there is, in fact, a decrease on treatment which continues to post-treatment.

[Slide.]

We examined other laboratory analytes and saw no differential effect in AST, hemoglobin, white blood cells, platelets and electrolytes.

[Slide.]

What I discussed with you now are some of the what we might call predictable adverse events, identifiable target organs. We also had to look for signals in our database of any issues that might be a concern. So, I have shown you here the rarely observed related adverse events in the database of 2,298 patients.

When we, including our safety officer, looked at these events and came up with these individual or infrequent adverse events which we thought we should bring to your attention, that is where there may, in fact, be some association that would need to be investigated further as we have more studies and postmarketing.

So we saw a few cases of anemia, thrombocytopenia and pancytopenia, one case of a hemolysis, actually after

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the NDA, and the others which you can see here.

[Slide.]

What are our conclusions about safety? The safety profile of Synercid is characterized as follows; the drug causes peripheral venous irritation. This is manageable to some extent and in some patients by an increase in dilution volume if their cardiovascular system will permit it or, when clinically indicated, central venous catheter administration can be used.

Arthralgias and myalgias are part of the safety profile of the drug. These are reversible and sometimes are treatment-limiting. Elevations in conjugated bilirubin occur. These, too, are reversible and are unaccompanied by evidence of hepatocellular toxicity.

We believe that, otherwise, there is a favorable cardiovascular, digestive, hematopoietic, hypersensitivity, metabolic, nervous-system and renal-safety profile.

[Slide.]

In conclusion, then, what are the primary data supporting the claims which Dr. Savarese mentioned to you at the beginning, in vancomycin-resistant *Enterococcus faecium* and *Staph aureus* indications failing or intolerant of other therapies. These all come from the emergency-use program and the same arguments, if you will, support them.

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First of all, the background is the in vitro microbiological data suggesting the likelihood of efficacy. Those are the patient populations for which other therapies were not appropriate or have failed. Assessment of response is performed in rigorously defined evaluable populations so that a treatment effect could be ascertained.

Efficacy was noted in varied clinical settings with a hierarchy of response rates that could be expected clinically. We saw consistent results across studies and across time. We demonstrated that eradication from the blood stream can be achieved. Our expert consultants tell us that this, indeed, is a clinical benefit.

The data should be interpreted in the context of the comparator studies demonstrating efficacy.

[Slide.]

Comparator claims. For nosocomial pneumonia, equivalence to vancomycin was shown for the primary efficacy parameter and this satisfies the single trial requirement. For complicated skin and skin-structure infection, equivalence to comparator was seen in each of each of two studies for the primary efficacy parameter.

For CAP, we did not demonstrate equivalence in one of the two studies but have submitted to you data showing efficacy against Strep pneumoniae in nonmicrobic infection

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as well in bacteriologic patients. Although this is post hoc analysis, we would ask you to consider whether this would represent a potential useful indication for clinicians basically treating Strep pneumoniae.

The safety profile, we believe, is favorable for patients in the indications claimed.

[Slide.]

Our conclusions overall. Synercid is a focused-spectrum antimicrobial agent. It represents a new class of antibiotics in the U.S. pharmacopoeia. It has in vitro activity against medically relevant, multidrug-resistant, gram-positive pathogens and we have demonstrated in vivo efficacy in diverse clinical settings and in very, very ill patient populations.

The epidemiologic context, the context described by Drs. Murray, Edmond and Gilbert, and the resulting medical need are reflected in the increasing demand for enrollment that we are seeing in our emergency-use program.

This first injectable straptogramin antibiotic will provide a therapeutic alternative to glycopeptides for the treatment of many multi-drug resistant gram-positive infections.

Thank you very much for your attention.

DR. SAVARESE: RPR would like to thank FDA for

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guidance during the development of Synercid especially their review of the clinical-study protocol design. RPR also thanks FDA for their expedited review of the clinical data which underscores the importance of making Synercid available to the medical community in as short a period of time as possible.

Thank you very much for your attention.

DR. RELLER: Dr. Savarese, the committee appreciates the focussed, crisp presentations. I should now like to open the floor to any questions to the sponsor related to the data presented, any clarifications.

DR. CHESNEY: I have one question for Dr. Talbot. Given the peripheral venous irritation, I wondered if you had any information about irritation following central venous administration. Has there been any increase in clot formation?

DR. TALBOT: That is a good question. We did wonder about that, ourselves. We looked at that in two different ways. First of all, we looked at the overall frequency of adverse events when the drug was given by central venous administration as compared to peripheral administration.

We were looking at the broad spectrum of adverse events and saw no difference related to the route of

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administration. We also looked at a subset of patients who had had autopsies following central venous administration. We obtained autopsy results primarily from our emergency-use studies and for the nosocomial pneumonia study.

These were very ill patients and we focussed specifically in our review on the cardiovascular system, the great veins and the lungs. In one patient, there was evidence of thromboembolic disease to the lungs but the investigator made it clear that this was, certainly, due to other causes and not related to the central catheter.

So, in that patient, there was no evidence of any involvement of the Synercid administration centrally with the event. And, in the other patients, there was nothing to suggest a problem. So the answer is we have looked and we see, in particular, no evidence of thrombosis at the central venous catheter site.

DR. RELLER: Dr. Talbot has just responded to Dr. Chesney's question about route of administration.

DR. PARSONNET: This is a question also for Dr. Talbot. I noticed in the emergency-use group that you allowed mixed infections for abdominal and skin infections, that some of those were actually VRE-plus organisms. I was wondering if you could tell us how Synercid did in those groups if you broke them down, so people with mixed

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infections versus people with just pure VRE.

DR. TALBOT: Yes. VRE, or enterococci in general, are often seen in polymicrobial settings, so we did look at that specifically. Overall, about one-third of the patients in the emergency-use program had polymicrobial infections. There was no difference in response rates between the patients with polymicrobial infection and monomicrobial infection either in univariate analysis or multivariate analysis.

DR. ARCHER: I have a question for Dr. Rhodes about drug-drug interactions and the cytochrome P450 system. I was wondering if you looked at any other drug-drug interactions, particularly macrolides, other protease inhibitors and rifampin.

DR. RHODES: We have done another drug-interaction study in vivo with nifedipine. The results are just being completed. We saw a drug-interaction, a 35 percent increase in nifedipine AEC. We are currently planning in vivo drug interactions in all these other drug categories.

We could say at the moment that we believe we have a relatively good in vitro to in vivo correlation. We have in-vitro- determined inhibition constants for Synercid with a variety of substrates and it would appear that the in vitro KIs will give us some rank order of the magnitude of

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effect in vivo but we still need to conduct those other in vivo drug interaction studies.

DR. ARCHER: Do you have any evidence that rifampin might actually decrease the Synercid levels when coadministered?

DR. RHODES: No, because Synercid really isn't the substrate for 384. Induction of 384 by rifampin should not affect Synercid plasma levels.

DR. NORDEN: This question is for Dr. Nadler. Harriette, first of all, is there any activity against H. flu which is not listed as susceptible?

DR. NADLER: There is modest activity against H. flu. The MIC90s have varied between 4 and 8 and I think in the community-acquired pneumonia program, there were very few failures due to the modest activity against H. flu.

DR. NORDEN: The follow up to that is, in your slide, Chlamydia and Mycoplasma are both listed as susceptible. Is there either animal data or intracellular activity that has been demonstrated that they may be susceptible as the Legionella as well in terms of in vitro--but do we know anything about in vivo?

DR. NADLER: We have conducted a study with Dr. Paul Edelstein in Philadelphia, legionellosis in the guinea pig. However, in the small animals, Synercid can be

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somewhat toxic. And so the animals had to be sacrificed too early to do a full determination of efficacy.

But what he did report was that there was less consolidation in the lungs when the animals were sacrificed. In addition, there was a several-log drop in the bioburden of the Legionella. But he could not do a complete efficacy analysis.

Further, we know from the intracellular killing in the ex vivo macrophage system that the Chlamydia are also found in the same place in the cell, the phagolysosomes, as the Staph. And so although Dr. Tulkens in Belgium didn't study Chlamydia specifically, he would expect that there would be intracellular activity against the Chlamydia as well.

DR. ARCHER: Did you see an mutation from inducible constituents of MLS during therapy with--for Staphylococci?

DR. NADLER: It was not seen in the clinical program.

DR. ARCHER: Did you look for it?

DR. NADLER: We examined any Staphylococci which showed a change in susceptibility during treatment.

DR. ARCHER: And you saw no--

DR. NADLER: No.

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DR. SOPER: The pharmacokinetic data you suggest is similar in men and women. How many women were in your study?

DR. TALBOT: We have a comparison of roughly, in normal volunteers, over 16 subjects. We completed recently a population pharmacokinetic analysis in over 100 patients.

DR. SOPER: How many of those were female?

DR. TALBOT: I would say--I will have to think of the actual number but I guess the best way to answer your question is there were a significant enough number of female patients for us to be able to pull out gender as a covariate in that analysis. And gender was not a covariate with respect to pharmacokinetics of either quinupristin or dalfopristin.

That wouldn't be anticipated based on what we know about the in vivo disposition of the drug and how it is cleared and metabolized. We would not expect, really, a gender difference.

DR. SOPER: I know you are not going after urinary tract and you showed good efficacy in this one study, but what happens to the drug in the urine? Most of it is excreted in bile or liver?

DR. TALBOT: Most of it is excreted in the bile. About 20 percent of the dose is excreted in urine. Some

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portion of that 20 percent excreted in the urine is active drug component. We have actually measured that in Japanese volunteers and we have active microbiological activity in Japanese volunteers.

DR. SOPER: At what concentration?

DR. TALBOT: I can't recall off the top of my--

DR. MONTAY: I am Dr. Guy Montay. We have urinary excretion data from the Japanese volunteers and we have seen in the 24-hour excretion that we have drug levels using bioassays which are above the MIC of susceptible--I mean above 0.5 to 1.0 mcg/ml of urine. We are planning a study in Caucasian subjects to assess what are the urinary levels of a drug in Caucasian subjects.

DR. CHESNEY: This is for Dr. Talbot, also. On your monomicrobial pneumococcal community-acquired pneumonia infections, I think you gave us this information in one of our handouts and I have forgotten, but how many of those organisms were penicillin resistant and do you know any of the ceftriaxone susceptibilities for those organisms?

DR. TALBOT: When we look at the pneumococci overall in our program which would come from the CAP in nosocomial pneumonia indications, there were very few overtly penicillin-resistant strains; four, I believe, four successes. So, of the very small number, we had 100 percent

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success rate as did the comparator regimen.

In terms of ceftriaxone, we did not characterize that when we checked with Harriette, but we characterized according to penicillin susceptibility and not ceftriaxone. Am I correct on that?

DR. NADLER: We had collected penicillin, ciprofloxacin, erythromycin, vancomycin and gentamicin on all the Strep pneumoniae.

DR. CHRISTIE: My question is for Dr. Rhodes. Regarding the pharmacokinetics of Synercid, I wondered about the eight groups of newborns, infants, children, adolescents. Do you have any information, please?

DR. RHODES: No. At the present time, we don't have any of pharmacokinetic data in pediatrics, younger patients.

DR. SOPER: As a follow up, how about pregnancy, potential teratology, that sort of thing? Any information there?

DR. RHODES: I think I will defer to my drug safety colleague on that question.

DR. RELLER: That is Dr. Soper asking the question. Please give your name for the recorder.

DR. PICAUT: I am Phillippe Picaut working in drug safety in RPR. I am in charge of the development of the

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compound. Regarding the teratology effect of Synercid, we have done some studies in rabbits, rats and mice and we did not observe any evidence of teratogenic potential for this compound.

DR. SOPER: Is there some experience in France in the oral agent given to pregnant women?

DR. PICAUT: Do you mean in pregnant women?

DR. SOPER: Yes.

DR. TALBOT: We are going to have to have a tag team here. What I can tell us you is that we just learned, in the emergency-use program in the states, of one woman who was exposed to Synercid when she was very early in gestation. Her pregnancy test was negative when she came in. She received Synercid and her pregnancy turned positive a couple of weeks later.

We had the information that she delivered uneventfully at term of a normal infant with a short exposure to Synercid. As for pristinamycin, I can introduce my colleague, Dr. Francois Bompert, who can speak to that.

DR. BOMPART: Thank you. I am Francois Bompert from RPR clinical development. Pristinamycin is approved in France for usage. I believe the labeling does not exclude children or pregnant women. There are negligible reports of usage in pregnant women and children so the labeling doesn't

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go as far as recommending usage in these situations but it does not contraindicate the usage in pregnant women.

DR. SOPER: But do you have any experience where patients have been exposed, reports with that agent, that we can get some information from?

DR. BOMPART: The available information in pristinamycin is scanty. There was one publication a few years ago, someone, including his own personal experience with the data, are way too anecdotal to report to the committee.

DR. DANNER: Is the drug compatible with total parenteral nutrition? Do you have data in patients on TPN who are also getting the drug in terms of liver toxicity? And then the second question is do you have information on drug clearance during hemodialysis or continuous hemofiltration?

DR. RHODES: I will try to answer the question on hemodialysis. We have not conducted that study per se but I think if you consider the molecular weights of dalfopristin and quinupristin, the standard sorts of calculations that are used based on creatinine clearance, factoring in molecular weight and factoring in free fraction of the drug, you would calculate that the hemodialysis of Synercid would be relatively low.

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That clearance would be maybe in the 25 to 40 ml/min range. But that is a clearance that is substantially lower than the actual systemic clearance of the drug. The drug will actually be cleared very rapidly. That has also been true in patients. We haven't seen extraordinary changes in patient profile with the pharmacokinetics of Synercid.

DR. RELLER: Dr. Rhodes responding to that question.

Dr. Savarese, again, thank you for the presentations and the answers to the specific questions about the data presented. This concludes the sponsor's presentation. We will have a 15-minute break and reconvene promptly at five minutes of 11:00 for the FDA presentation.

[Break.]

DR. RELLER: We will now have the presentations by the FDA. We will adjust the lunch hour as necessary to give adequate time for the FDA presentations. It is unlikely that the entire time for the open public hearing will be required so we will make up whatever time is necessary to keep on schedule and have the proper amount of time for a full and complete discussion of all of the data and the questions posed to the committee by the FDA.

Dr. Fred Marsik, microbiologist with the FDA, will

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present the FDA's assessment of the microbiology of the compound under consideration.

Fred?

FDA Presentation

Microbiology

DR. MARSIK: Thank you, Dr. Reller.

[Slide.]

Members of the advisory committee, RPR members, audience, I would like to present to you the microbiology data as seen by the FDA. I am a microbiology reviewer for the NDA submitted by RPR on Synercid.

[Slide.]

First of all, just to refresh you on some of the information that Dr. Murray gave us in the epidemiology. *E. faecium* accounts for about 5 to 10 percent of the isolated enterococcal species that was seen in the clinical situation and the resistance to vancomycin could be from 2 to 5 percent in most areas although some geographical regions will run higher in this situation.

Also it is interesting to note that greater than 90 percent of the *Enterococcus faecium* are resistant to erythromycin.

[Slide.]

As you have heard, Synercid is a combination of

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two components, quinupristin as well as dalfopristin. Each one of these does have active metabolites in humans and these are listed on the board. This activity tends to vary depending on the organisms against which these metabolites are tested but, in the case of quinupristin, there are two main metabolites, RP 69012 which tends to be about two times more active than the parent compound as well as the RP 100391 which is also about two times as active as the parent compound, depending again on the organisms against which it is tested.

[Slide.]

In the case of dalfopristin, there are also two metabolites that are recognized in humans, RP 12536 which tends to be about twofold less in activity than the parent compound and RP 46790 which can be twofold to greater than fourfold more active than the parent compound against specific organisms.

So these two metabolites from each of these various compounds do have some activity against organisms.

[Slide.]

As we have heard, the mode of action of quinupristin and dalfopristin is an inhibition of protein synthesis. The interesting thing about this is that this protein synthesis inhibition occurs at two different sites

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on the ribosome with dalfopristin bringing about confirmational change in the ribosome allowing for greater affinity of the quinupristin to act at the ribosomal site on which it attaches.

In vitro in animal models it has been shown that the ratio of quinupristin to dalfopristin--there is a very wide range in that ratio, anywhere from 16:84 to 84:16 in which the synergistic activity of this combination was actually seen.

However, in animal models of endocarditis, show the importance of the dalfopristin component of the combination especially against the constitutently resistant, when MLSB Staph aureus has been noted in the application. It is very important to have the correct concentration. Dr. He Sun will address some of the pharmacokinetics of that in the next presentation.

[Slide.]

The drug, itself, has been shown to be cidal in certain organisms and static against others. It has shown to be bacteriostatic against Enterococcus faecium. The demonstration of whether the drug is cidal or static depends on the laboratory methodology that is used. Dr. Moellering, in a very recent paper--in fact, December of 1997--his group stressed the importance of various test procedures to be

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used to actually show whether the Synercid is cidal or static against organisms.

We know that it is bacteriostatic against *Enterococcus faecium*. That has been well documented. Whether it is bacteriostatic or bacteriocidal, against, against some of the constitutently resistant strains of *Staph aureus* in vivo is a question that is not fully answered at this time.

[Slide.]

The MIC:MBC ratios against various organisms differs. Here you can see that, in the case of *Enterococcus faecium*, it is generally a ratio of greater than 4. When you talk about the vancomycin-resistant *Enterococcus faecium*, it is greater than 8. *Staph aureus*, greater than 2. The constitutently resistant *Staph aureus* as well as *Staphylococcus aureus* that are resistant to methicillin, greater than 4. And for *Streptococcus pneumoniae*, generally that ratio is about 2.

[Slide.]

As noted before, in endocarditis models, particularly those which have been induced by the constitutently resistant *Staph aureus* as well as the inducibly resistant *Enterococcus faecium*, there is decreased activity of Synercid in reducing the numbers of organisms in

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the vegetations that are cultured.

In fact, this has led various investigators to suggest that, perhaps, in certain cases, really, the AUC over the MIC in quinupristin, may be a better indicator of the efficacy against certain strains of *Staphylococcus aureus*.

What has been used to determine the efficacy of the compound is the agency over the AUC over the MIC in which this has been found in animal models to correlate very nicely with efficacy but, in humans, this data is not fully developed as of this time.

[Slide.]

One of the interesting things about Synercid is that it has a long post-antibiotic effect. This has been shown, however, to vary by the various organisms against which this is actually developed. In the case of *Streptococcus pyogenes*, you can see the post-antibiotic effect is about 18 hours. In *Streptococcus pneumoniae*, it is approximately 9 hours; in *Staph aureus*, 4.

For the Enterococci, we see a decrease in the post-antibiotic effect and then, as we get into the vancomycin-resistant *Enterococcus faecium*, as well as constitutently resistant *Staph aureus*, the post-antibiotic effect does decrease.

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[Slide.]

This post-antibiotic effect has been shown in recent data provided to us to be dose-dependent but there is very limited in vivo post-antibiotic effect data that has been available to date.

[Slide.]

A number of resistant mechanisms can occur in the Enterococci as well as Staph aureus. These can be enzymatic, efflux, target modifications as well as intrinsic resistance which is probably the mechanism of resistance of Enterococcus faecalis to Synercid, although this has not been fully explored and the actual mechanism of resistance in faecalis is not understood at this time.

Enzymatic resistance in Staph aureus can be due to quinupristin hydrolysis and, in the case of dalfopristin, acetylation of the compound, itself. These have been shown to be related to certain genes within these organisms; the vgb gene, the vatB genes in Staph aureus.

In Enterococcus faecium, dalfopristin has been shown to be inactivated by acetylation which is mediated by the satA gene.

[Slide.]

In the case of efflux in Staph aureus, dalfopristin efflux is mediated by the genes vga, msrA. The

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msrA is actually inducible by erythromycin but not by quinupristin but may be to resistance to quinupristin when induced by erythromycin.

[Slide.]

There are target modifications also that can occur in Staph aureus; methylation of the ribosome mediated by the ermA and ermC genes. Again, this can be induced by erythromycin but not by quinupristin. Generally, you see this inducible methicillin, inducible MLSB phenotypes and quinupristin may not be affected in these particular cases.

[Slide.]

Target modification occurs in Enterococcus faecium by methylation of the ribosome which has been shown to be mediated by the ermAM gene and this can be induced by either erythromycin or quinupristin. So we see that there is a possibility for certain organisms to become cross-resistant to macrolides, lincosamides and streptogramin Bs. Some of this resistance has been shown to be transferrable by genetically.

In the clinical studies, we have not seen any direct evidence that there actually has been a conversion of an inducibly resistant MLSB strain to constituent resistance, this certainly has been shown to happen with certain in vitro as well as other situations.

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Dalfopristin resistance, generally, tells you that organisms will be resistant to the quinupristin but, if the organism is resistant to quinupristin, it does not mean that it will be resistant to the dalfopristin and, in actually, if you combine the two against the quinupristin-resistant organisms, you do get activity of Synercid.

In vitro development of resistance has been shown in a recent paper to Synercid simply by training the organisms to grow in increasing concentrations of the combination of quinupristin and dalfopristin.

Interesting in this was the fact that those organisms that developed this resistance to greater than or equal to 8 mcg/ml generally were stable; that is, when you removed the antibiotics, these organisms tend to stay resistant to the Synercid. When there was an MIC of less than 8, around 4 mcg, organisms generally reverted back to susceptibility after the Synercid was removed.

Whether these organisms were present in the environment is not fully known but it is felt that, perhaps, one of the mechanisms for resistance in these stably resistant organisms already exists allowing them to become stably resistant to the combination of quinupristin and dalfopristin.

We have seen in vivo development, as was noted by

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Dr. Talbot. This has been, in some patients with Staph aureus as well as with developing resistant of some Enterococcus faecalis which is intrinsically resistant to the combination to begin with, not an indication for treatment.

The importance of maintaining peak concentrations of above the MIC to inhibit the development of resistant organisms has not been fully explored and is a question that still remains to be answered.

Component resistance? Certainly, there is resistance in quinupristin with Synercid as well as some organisms being resistant to dalfopristin, also. Organisms can become resistant to high concentrations of quinupristin but still remain susceptible to the combination of quinupristin and dalfopristin.

[Slide.]

For susceptibility testing, testing is generally done at the 70:30 ratio, 70 parts of dalfopristin to 30 parts of quinupristin, both for MIC and disk susceptibility testing. In vivo animal data suggests that certain organism phenotypes such as your constitutently resistant Staph aureus which have been shown to be more refractive than animal models to Synercid may not actually be delineated by the proposed interpretive criteria which I will show you on the

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next slide.

So there may be subpopulations or organisms within certain groups that you may not be able to differentiate by MIC or disk susceptibility testing. This has led to the suggestion of actually testing with the individual components, dalbavancin or quinupristin, rather than the Synercid combination. But little data is available on this type of information with susceptibility testing of just dalbavancin or quinupristin.

[Slide.]

These are the suggested susceptibility testing interpretive criteria at this time, with an MIC of less than or equal to 1 mcg/ml indicating susceptible and greater than or equal to 4 mcg/ml equaling resistance. But, as indicated on the previous slide, there were some questions as to whether this will pick up some of the organisms in which there is reduced activity of Synercid against.

That concludes my presentation.

I will now ask Dr. He Sun to discuss the pharmacokinetics.

Biopharmaceutics

DR. SUN: Good morning. My name is He Sun from the Office of Clinical Pharmacology, FDA.

[Slide.]

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I will discuss the clinical pharmacology section for Synercid.

[Slide.]

The discussion will focus on the following three topics: the differences in the elimination, distribution, and accumulation kinetics of quinupristin and dalfopristin, the dose adjustment issues for hepatic impaired patients, and the potential drug-drug interactions.

[Slide.]

As a background review, we can see the two compound components for Synercid, Q and D, has dual mode of action. The combination of Q and D is synergistic. Synercid is 16-fold more potent than Q or D alone, and the presence of D is important, although the effective ratio for these two components wide.

Metabolites of Q and D contribute to the synergy. Most MIC-90 we consider as 1 mcg/ml and the PAE values are concentration dependent, organism dependent, and phenotype dependent.

Clinical usage for this drug will be mainly for seriously ill patients, and the Synercid inhibits CYP3A4 enzymes.

[Slide.]

So, bear this background in mind. We consider the

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combination of Q, D, and their active metabolites is needed for synergistic activity at the site of infection.

Pharmacokinetic profiles of Q, D, and metabolites may be important in seriously ill patients, and dose adjustment recommendations may be complicated.

[Slide.]

Now, let's go over some pharmacokinetic profiles for these two compounds Q and D. The plasma clearance for these two components are almost equal, however, the half-life, volume distribution, and accumulation ratios for Q are always greater than D.

[Slide.]

This concentration-time profile for these two components after giving 7.5 mg/kg dose, q12 multiple dose for 4 days. This red line is the concentration profile for D and the green curve is for Q.

We can see here the half-life for Q is longer than that of D. This means at a certain time, the concentration of Q may present in the tissues or plasma while D disappeared.

[Slide.]

Again, this is a concentration of Q, D, and their metabolites. The same phenomena was seen here. The red curve which is concentration for Q and metabolites maintain

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much longer than that of the green curve, which is for D and the metabolites.

[Slide.]

Again, let's consider the concentration of D is necessary to produce synergistic activity combined with Q. This comparison of volume distribution across different studies, this is data from six different studies. The blue bar represents the volume distribution for Q, and the red is for D. We can see here the volume distribution for Q is always near double than that for D. This means the distribution for Q is much wider compared than that of D.

This might suggest that in certain tissues, you will only see the concentration for Q rather than D presented in combination.

[Slide.]

After giving multiple doses, the plasma drug accumulation for these two components are different. Again, the blue bar is for Q, and the red is for D.

These two are the comparison of Q in terms of AUC value change after first dose and multiple dose. The increase for Q is doubled after multiple dose compared to single dose. Again, for half-life, the increase for Q is doubled after giving multiple dose. However, this change for D is less significant as that for Q. So these further

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support the suggestion that Q may distribute deeper in certain tissues, although the half-life is only around one hour, however, after multiple dose, even given q8 hours or 12 hours, you still see significant accumulation in plasma, so it probably is a drug of Q released from certain tissues, and the half-life increase after multiple dose, single dose, for D is increased much more than that for D.

[Slide.]

If we look at the combination of Q, D, and their metabolites, the similar phenomena is still seen here. The AUC changes for Q is doubled after multiple dose and single dose, and the half-life is doubled, but less change for D in terms of AUC and half-life.

[Slide.]

This is a comparison of the drug tissue distribution, the plasma/blister concentration measurement. In plasma, the blue bar in plasma, this is for Q, this is for D, so the ratio for these two components in plasma, the AUC values is 3 to 7 ratio, however, you see that AUC value in blister for these two components only is a 1 to 1 ratio.

Again, in terms of Cmax, the value for quinupristin and dalfopristin is 3 to 7 ratio. The concentration of Cmax for these two components in plasma fluid is nearly on a 1 to 1.5. These means that it required

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a high concentration to produce higher concentrations of dalfopristin in plasma fluid or tissues.

[Slide.]

Now, let's go over some kinetic profile in patients with liver function impairment. This study was in 16 patients with a Child-Pugh A score or B score compared to 17 normal health volunteer subjects.

The clearance for Q and metabolites are markedly decreased, while the clearance for D are maintained unchanged. This gives a concern that in this type of patient, the concentration maintained in patient plasma or tissue compared to the other for D, the difference is enlarged because the clearance of Q being more decreased while D has no change.

[Slide.]

Again, if we review this graph, we see AUC value for Q in hepatic-impaired patients increase by 180 percent, while for D, only increase around 40 percent. So, the hepatic impairment has a significantly more effect on Q and metabolites compared to that for D and its metabolite.

Bear in mind that the Q will produce a significant bactericidal activity in the presence of D. This shows that in this type of patient, the Q may prolong in tissues or plasma in certain conditions.

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[Slide.]

Drug-drug interaction issues. As we reviewed before, Synercid significantly inhibit CYP3A4 enzymes, and both Q and D are potent inhibitors of cyclosporine metabolism in vivo.

Also, it is expected that Synercid will inhibit other drug metabolism of CYP3A4 substrates.

[Slide.]

A study demonstrate in 24 subjects with 7.5 mg/kg dose of Synercid given q8 for 2 days, and on day 3 give 300 mg cyclosporin, we see a significant increase of AUC for cyclosporin by 63 percent, an increased Cmax by 30 percent, half-life by 77 percent, and decrease of clearance for cyclosporin.

[Slide.]

In summary, Q and D have different elimination, distribution, and accumulation kinetics. As compared to dalfopristin, quinupristin has longer half-life, larger volume distribution, and higher accumulation ratios.

[Slide.]

Q may distribute more widely, deeper, and more homogeneous than D in tissues. Tissue distribution kinetics, as demonstrated in blister fluid concentration, shows that when plasma AUC and Cmax of D/Q is 3 to 7 ratios,

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blister fluid concentration and AUC only reach 1 to 1.

[Slide.]

In terms of dose adjustment, in hepatic-impaired patient, the kinetic difference between Q and D is enlarged, and the plasma Q concentration to be more affected than that of D. Therefore, dose adjustment requirement is required, however, the strategies for these hepatic-impaired patients need to be further considered.

[Slide.]

In drug-drug interactions, close clinical monitoring of cyclosporin and other CYP3A4 substrate is necessary. In this consideration, the level and concern should be considered.

This concludes my presentation. I will turn it over to Dr. Rakowsky for clinical section.

VREF/Hospital-Acquired Pneumonia

DR. RAKOWSKY: My name is Alex Rakowsky. I am a medical officer in the Division of Anti-Infective Drug Products.

[Slide.]

I would like to thank the entire review team to start things off. This would be a good opportunity to do this. Before thanking the review team at this time, I would also like to thank all prior reviewers, which are just too

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numerous to name. We are a fairly young bunch when it comes to the present review.

In Pharmacology and Toxicology, Dr. Kenneth Seethaler and his team leader, Dr. Osterberg. Dr. Marsik, you have met already, and his team leader, Dr. Sheldon. from Chemistry, Dr. Timper and his team leader, Dr. Katague.

For Biopharmaceutics, Dr. He Sun, who just spoke, and his team leader, Dr. Frank Pelsor. For Clinical, Dr. Susan Thompson and myself will do the presentations, and that's me on the bottom. Mr. David Bostwick helped with the safety review. Our team leader is Dr. Rosemary Roberts, division director Dr. Gary Chikami. Finally, from Biostatistics, Dr. Liji Shen, who was very helpful in data analysis, and his team leader, Dr. Daphne Lin.

[Slide.]

I would like to use two slides to give a brief overview of the clinical studies, and they are purposely split up into two slides. Dr. Thompson will present the studies with the q12 dosing regimen, namely, the community-acquired pneumonia and complicated skin and skin structure, and I will work on the VREF studies which are essentially q8 and hospital-acquired pneumonia.

For VREF, there are four studies done, open-label, no comparator. Primarily a q8 dosing regimen was used at

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7.5 mg/kg/dose, and again primarily VREF, which I will use as a synonym for vancomycin-resistant enterococcus faecium, but other gram-positive pathogens were allowed in all but study 301.

Hospital-acquired pneumonia had one study, open-label, with a comparator, and again 7.5 mg/kg/dose q8.

[Slide.]

Both community-acquired pneumonia and complicated skin and skin structure had two studies. Both were comparative. One study in community-acquired pneumonia was blinded, the other three studies were open-label. Again, both of these indications utilized a q12 dosing regimen of 7.5 mg/kg/dose.

[Slide.]

To get into the VREF studies, I just want to raise several issues prior to going into the data. As had been mentioned by Dr. Murray and by Dr. Talbot, difficult studies to analyze due to multiple reasons, and this is a summary of at least some of the major issues.

First, this is a non-traditional approach to approval for this division. It is pathogen driven and not site of infection driven. As had been mentioned before, there are issues of the historical control and these studies were uncontrolled in nature.

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The patient population, though, that was expected to be enrolled, had an expected high mortality rate, multiple comorbidities, concomitant illnesses, et cetera, and because the studies were basically driven by specific sites of infection or indications, you expected different efficacy and mortality rates depending on the severity of the site of infection, which leads to problems in terms of intra-study consistency.

In addition, as will be noted in the next few slides, the studies were designed slightly differently depending on the emergency basis of the studies, and therefore, adequacy of documentation varies between the studies leading to inter-study consistency problems.

[Slide.]

In order to try to rectify some of these issues prior to looking at the patients, initially, stringent evaluability criteria were defined for each indication. As Dr. Talbot had mentioned, I will try to present differences between our review and the sponsor's review, again not implying that one is correct or the other is incorrect, but essentially for a new indication, trying to give different approaches to the data analysis.

Also, I stress the word "stringent." The mind-set that was taken with this initial approach to review was that

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we were interested in the patients where we could have the best feel for what the effect of Synercid was in the treatment of the infection.

In addition, there was an analysis of the patients who died on therapy and who were found unevaluable based on these criterion, and lastly, there is overall assessment of the mortality rates was just a crude mortality rate.

The next four slides will give you a historical perspective of the studies that were done.

[Slide.]

Study 399, as has already been mentioned by Dr. Talbot, was a collection of the initial emergency IND experience for the treatment of VREF and other gram-positive pathogens. The data was collected retrospectively, 227 patients at 159 study sites in 6 countries, and as expected with the emergency IND collection, the adequacy of documentation was highly variable.

[Slide.]

Study 301 was a prospective study designed by the sponsor with FDA input. The sole pathogen allowed was VREF, again faecium. Strict documentation was required as seen in the case report form submitted with the study protocol.

The endpoints chosen per indication. What I mean here is per site of infection, were consistent with FDA and

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IDSA guidelines. The study centers were chosen by the sponsor as appropriate study centers so as to fulfill this requirement, 265 patients at 44 study centers all in the U.S.

[Slide.]

Study 398, also called 398A, similar in nature to 301, again a prospective study with strict documentation required. The two major differences, first, other gram-positive pathogens were allowed in addition to VREF. Also, the endpoints were more variable than 301, but overall still consistent with FDA and IDSA guidelines. The number of study centers is as shown, of 219 patients enrolled in 6 countries.

[Slide.]

Lastly, 398B, run under a treatment IND and again a prospective study. As with 398A, primarily VREF infections, but other gram-positives allowed.

Documentation requirements were less stringent and a major issue was that the end-of-therapy endpoint was most commonly used by the investigators on real patients. 528 patients at 267 study centers in 6 countries.

[Slide.]

Just to give a brief overview of approach to the summary of studies, the emphasis will be on the two

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well-documented, prospective studies with adequate endpoints, namely, 301 and 398A. In the slides that follow, I will refer to 398A as just 398, however data from 399 and 398B will be presented, as well, for overall summary.

We will start off with discussion of some of the general inclusion, exclusion, and evaluability criteria followed by overall summary of results and mortality rates, and then going into the specific indications, this being done again because of the expected variable efficacy rates and mortality rates seen depending on the severity of infection.

There will be an emphasis on the vascular infections, namely, infections where a positive blood culture was required to enter a patient, namely, bacteremia of unknown origin, central-catheter related infections, and a brief overview of endocarditis where a small number of evaluable patients were found, and also the four other most common infection sites, intra-abdominal, bone and joint, skin and skin structure, and UTI.

In addition to these, there are four to five more per study, but the numbers, again, this would have been overwhelming to present all of them.

[Slide.]

The inclusion criteria listed are just the basic

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criteria needed to be enrolled in the studies. These last two apply to all the studies except for 301.

In order to be enrolled, you can have either a documented infection with VREF, and this was defined as resistance to vancomycin greater than or equal to 8 mcg/ml. For other patients who had a gram-positive pathogen other than the VREF, if the patient had a pathogen that was resistant to or having intermediate susceptibility to all available clinically appropriate antibiotics, that could enroll a patient.

If these two did not fit, then, the third category was for patients who had a non-VREF pathogen that was susceptible to available antibiotics, but the patient had either documented intolerance or an absolute contraindication to those.

[Slide.]

I just bring up two exclusion criteria of note. The first, each protocol specified that underlying disease with expected survival less than one week was an exclusion criteria, but as will be seen, a large number of patients did die during the study, and a large percentage of this died in the first week of therapy.

Secondly, prior enrollment in a Synercid study was used as an exclusion criterion by the medical officer.

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[Slide.]

These evaluability criteria, this slide essentially stresses three differences between the medical officer and the sponsor. Dr. Talbot had talked about these two, so I will briefly mention them.

The medical officer found anybody evaluable who received at least three full days of antibiotic therapy, and the follow-up visit was defined as at least five days after the completion of therapy except for indications where a longer endpoint is needed, such as endocarditis or bone and joint.

Another difference was for the use of clinically appropriate antibiotics to which the strain, be it VREF or other gram-positive pathogens, were susceptible. This was mentioned by Dr. Talbot as well, however, I included it in those patients who received these antibiotics prior to the initiation of Synercid.

The next two slides will deal with criterion that were used by both the sponsor and the medical officer. I bring them up due to the unique nature of them. Again, looking at stringent evaluability criterion, in order to be found evaluable, patients had to have a standard of care procedure performed as the four scenarios here or four examples.

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[Slide.]

For a patient with an abscess or a similarly infected collection of fluid, surgical drainage had to be done either prior to or early on in the treatment course. The same goes for infected tissue or bone with adequate debridement.

For infected hardware, removal was expected except in cases where the goal of antibiotic therapy was to avoid such removal. Unfortunately, the protocols or 301 and 398A were not specific, and I will get into more details in a few minutes.

Lastly, for intra-abdominal infections, if there was an anastomotic breakdown, biliary duct leakage, et cetera, then, some sort of surgical repair to rectify this was expected.

[Slide.]

Similarly, patients who died of multi-organ failure--and again assuming that this is after three full days of therapy in order to be found evaluable on that criterion--with neither documented persistence of VREF nor of clinical suspicion on the part of the primary investigator that VREF infection led to the patient's demise were called unevaluable.

So, a large proportion of patients who died on

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therapy were in the long run called unevaluable.

[Slide.]

With this in mind, these were the overall evaluability rates seen in the studies 301 and 398. Just briefly, for the advisory committee, the briefing package had sponsor's number for clinically evaluable. This slide will stress the fully evaluable patients, and the sponsor recently submitted this including these slides. So, this is again fully evaluable patients.

Medical officer for Study 301 found 46 percent fully evaluable, and the sponsor, a similar number.

Study 398, 33 percent, and 28 percent as per the sponsor.

[Slide.]

Overall efficacy rates comparable in Study 301, 56 percent with 65 out of 117 found either cured or improved, and also with the bacteriological cured or improved, so an overall response of 56 percent, as per the sponsor, 64.

Some more difference in Study 398, but again larger numbers in Study 301.

[Slide.]

To briefly touch on the other two studies, Study 399, as Dr. Talbot had mentioned, none of the patients were found evaluable by the sponsor. The medical officer found

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36 of them fully evaluable.

As for Study 398, 14 and 40 percent.

[Slide.]

Efficacy rate 64 percent for Study 399; 398B, 48 percent and 72. Again, differences in the evaluability rates leading to some of the differences in the efficacy rates seen.

[Slide.]

Mortality rates. This is just crude mortality for all the studies. This is based upon a denominator of all enrolled patients, and it is pretty tight, between 49.5 and 54 for all four studies.

[Slide.]

With this in mind, going through the basic criteria and overall summaries, it is only fair to go through some of the indications to see the actual effects of the variable mortality and efficacy rates seen in these indications.

They will be presented for each indication or evaluability criterion that seem to differ and then go into the efficacy rates.

Specific evaluability criterion used by the medical officer for bacteremia of unknown origin. Two blood cultures drawn from separate locations, with a central

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catheter culture not being accepted, at separate times, with pure growth of VREF.

No source of infection found on an adequately performed search for such a focus.

[Slide.]

The number of evaluable patients again comparable between the sponsor and the medical officer for the fully evaluable patients.

[Slide.]

Reasons why unevaluable, and I stress that these are the primary reasons why. Died during therapy is by far the number one reason in both studies. Also, lack of bacteriological confirmation based on the evaluability criteria mentioned prior accounts for 14 and 16 patients in the two studies respectively

I do mention the fact that these are primary reasons, and patients could have fallen into one of these categories and still died during therapy and be found unevaluable, and this will make more sense in a few slides.

[Slide.]

Specific efficacy criteria. Namely, criteria to be found a cure. Negative blood cultures from a peripheral site for two days in a row while on therapy. Again, a follow-up visit at least five days after completion of

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therapy with a negative blood culture. As noted before, no focus of infection seen that could be deemed as a seeding of the VREF bacteremia.

[Slide.]

These are the efficacy rates shown. I do want to stress that the patients found evaluable by the medical officer and the sponsor do differ, and therefore, this isn't an analysis of the same patients. For Study 301, the rates are comparable.

[Slide.]

This slide deals with patients who were found unevaluable and also died while on therapy or immediately after therapy. So, these are patients who were found unevaluable. Patients who died on therapy and were considered failures have been already shown in the prior slide.

We looked at these patients, looking at four different categories. The first category is a positive culture at the time of death. Again, these patients were not considered to be failures due to applicability of other evaluability criteria, such as dying before the third day of therapy was completed.

The next category is no repeat blood cultures were done prior to death after the initial entry culture. Again,

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these are more strict as we go up.

The next is the last negative culture was negative, and lastly, the last two or more blood cultures prior to death were negative for VREF.

Looking at Study 301, of the 35 patients found unevaluable and who died on therapy, 30 of the 35 had either one or more of their last cultures negative for VREF growth, while for Study 398, 13 of the 25, if I do my math right, fell into those two categories.

[Slide.]

Next infection is central catheter. The difference between the sponsor and medical officer, if the catheter was removed prior to Synercid initiation, then, the medical officer required at least one positive blood culture prior to study initiation and after the catheter removal to see that the infection was still carried through.

[Slide.]

Evaluability rates were very similar for the fully evaluable patients.

[Slide.]

Again, reasons why unevaluable. I stress died during therapy. Again, no positive culture pre-therapy commonly seen in situations where a catheter was pulled and there was either no repeat culture done after the pull or

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there was a negative culture after the catheter was pulled prior to study initiation.

[Slide.]

In order to be found a cure, there needed to be documented blood cultures for two days and at the follow-up visit, as the case of bacteremia, no seeding noted at focus of infection, and if the catheter was not removed prior to therapy, then removal during therapy was seen as a failure, a controversial point since the standard of care now appears to be removing the catheters, however, at Study 301 and 398, the investigators commonly were trying to salvage the catheter. I will get into that in a minute here.

[Slide.]

For Study 301, 5 out of 9, and 7 out of 9 cured. One out of these 4 failures in the medical officer arm were considered to be a failure due to this criterion. In Study 398, 4 out of 6, and 5 out of 5, 1 out of the 2 failures here was considered a failure due to the removal of the catheter while on therapy.

[Slide.]

Again looking at the patients who died on therapy and who were considered to be unevaluable, all 6 of those patients had at least their last 2 or more cultures negative for VREF at the time of death, and 10 out of 12 in Study 398

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had at least one or more of their last cultures negative for VREF prior to death.

[Slide.]

Endocarditis, again small numbers. One evaluable patient in 301 and a failure considered in both. Study 398, 4 evaluable patients, 1 out of 4, and 2 out of 4.

I want to get into the four other large indications at this time.

[Slide.]

The first is intra-abdominal infections. Really no differences from the sponsor. Again, I bring up the standard of care surgery evaluability criterion that was mentioned before. It was an important criterion used in this indication.

[Slide.]

Large numbers of patients enrolled in both studies, 46 out of 89 found evaluable by the medical officer in 301, and 43 out of 89 by the sponsor. Study 398, 21 and 17 out of 59.

[Slide.]

Again, one of the major reasons for unevaluability was died during therapy, however, as seen here, inadequate drainage or inappropriate surgical procedure did account for approximately 10 patients.

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In addition, I bring this category up, there are 9 patients for which it was difficult to interpret the final results due to lack of information on the CRF.

[Slide.]

Specific efficacy criteria. I just bring up the situation if subsequent surgery or daily debridements were seen as standard of care, that patient was seen as still evaluable. If there was no explanation for subsequent surgery, then the patient was seen as a drug failure.

[Slide.]

Efficacy rates again, for 301, fairly tight. More difference in Study 398.

[Slide.]

Bone and joint infections. In this one study, one major difference between the sponsor and medical officer was that any use of adequate prior antibiotics were prohibited. This really played more of a role in Study 398A where patients were initially started, for example, on the vancomycin, developed an allergy or intolerance, and then were switched to Synercid. For those patients, they were found to be unevaluable.

[Slide.]

Patients enrolled, again fully evaluable.

[Slide.]

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In order to be found a cure, after initial debridement, as was the case with intra-abdominal, any further surgical intervention was seen as a failure except in cases where multiple debridements were considered standard of care.

As was the case with central catheter, if there was a prosthetic infection, the goal of the therapy appeared to be to prevent the removal of the prosthesis, again controversial, however, the removal of the prosthesis in this analysis was seen as a failure of study drug.

[Slide.]

Let me account for those patients. One out of the 3 failures here was found a failure exclusively because of this criterion, and 1 out of the 2 failures here fell into that category.

[Slide.]

Complicated skin and skin structure. Slightly stricter definition of how the microspecimen had to be obtained.

[Slide.]

Number of patients enrolled, 25 in 301, and 16 in 398. The same number of evaluable patients in 398, 10 and 15 for Study 301.

[Slide.]

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The differences in the 5 patients fall in these four categories. Lack of information of which the medical officer could make a decision accounted for 3 out of those 5. Lack of a follow-up visit for 1 out of the 5. Poor documentation of a positive culture pre-therapy for the last of the 5.

[Slide.]

As has been described before, any surgical drainage of the infected site was seen as a failure except where daily debridements or further surgery was seen as standard of care.

[Slide.]

Efficacy rates are as shown, again fairly tight for 301 and small numbers for 398.

[Slide.]

Lastly, urinary tract infections. Differences between the sponsor and medical officer. Medical officer required greater than 10^5 cfu/ml of VREF, which had to be pure growth regardless of specimen type or regardless of patient.

[Slide.]

Number of patients enrolled 26 and 12.

[Slide.]

In order to be found a cure, it was required that

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there was less than or equal to 10^3 cfu/ml of VREF on urine culture done at test of cure visit, test of cure being defined by standard Points to Consider and IDSA guidelines for this criteria.

[Slide.]

Efficacy rates, again small numbers for 398, but no failures. Study 301, 65 percent and 81 percent for the medical officer and sponsor respectively.

[Slide.]

To get into the issue of MRSA, again Study 301 exclusively enrolled patients with VREF infections. The other three studies could enroll other gram-positive pathogens. It appears that there were 77 patients with a documented MRSA infection at the time of enrollment in these three studies. The medical officer found 14 of these evaluable, the sponsor found 20 of these fully evaluable. Ten of the 14 were bone and joint infections. The cure rate was 9 out of 14 or 64 percent. Again, a large difference between the number reported and the actual number found evaluable, usually again due to the nature of these two studies, a lack of documentation.

[Slide.]

Adverse events. I won't go through all of them, just some of note. Again, arthralgias and myalgias as

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mentioned by Dr. Talbot. The percentages you have seen before for each one, 13 percent had at least one of these two adverse events. Study 301, which has the best documentation for adverse events, the rate was 30.2. Usually, it was described at moderate in severity, however, in Study 301, there was a larger proportion of patients that described it as severe.

Overall, 4.4 percent of patients were d/ced due to these adverse events as being at least one reason for discontinuation. As mentioned by Dr. Talbot, etiology is not clear. More work is being done on it, and it appears to be reversible.

[Slide.]

Liver function abnormalities. There were 32 patients where a liver function abnormality was listed as at least one reason for discontinuation, and the sponsor has presented the bilirubin and the ALT-AST abnormalities as seen before, and no additions to that.

[Slide.]

Drug-drug interactions. As Dr. Sun had mentioned, there appears to be an effect on one of the metabolites of the p450 system. Alterations in cyclosporine levels were noted by several investigators in their patient narratives, however, this was not systematically studied in these

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trials.

[Slide.]

Lastly, the resistance issue. Development of VREF resistance, as seen by MIC increase against Synercid was seen in a low percentage of patients, usually found in stool surveillance cultures. The actual denominator is not known for two reasons: one, stool surveillance cultures was not required, and was done sporadically by the investigators, asked for the investigators' opinion, and secondly, for several of these cultures, MIC-Synercid were not done. The sole purpose of these cultures was to see a continuation of VREF in the stool was still noted.

[Slide.]

Just several issues to bring up again. We have seen these before, but to now bring them up after looking at the data.

Again, uncontrolled studies, and as Dr. Murray had so well put this morning, a lot of inconsistency in regard to treatment regimens in the literature, definitions of infection type, endpoints, et cetera. This really impacts on what to make of the efficacy rates, as well. We believe that they should be viewed differently based upon the severity of the indication, however, the literature primarily addresses bacteremia, but of note, it is not

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necessarily of unknown origin, which makes it even more difficult to use this data to tie onto efficacy rates seen.

Variable evaluability and efficacy rates among the various indications.

[Slide.]

The mortality rates seen for all four studies was fairly tight, around 50 percent. The literature range--this morning we saw 17 to 100--most articles with larger numbers seem to range between 30 and 70 percent, however, are we dealing with the same populations as these articles is difficult to tell.

Lastly, how do we interpret the data on the clearance of bacteremia for patients who are unevaluable and who died on therapy?

[Slide.]

Single study, Study 306. Open-label, comparative study. For both arms, aztreonam was added at 2 grams Q8, and it was Synercid, as noted before, at a Q8 dosing, and vancomycin of 1 gram Q12. It should be noted that the vancomycin levels were to be monitored during the study and the dose adjusted appropriately.

[Slide.]

Seventy-four study centers in 5 countries.
Enrolled 298 patients with the majority enrolled in the

United States.

[Slide.]

This lists some of the real basic clinical evaluability criteria, and lists one where the medical officer and the sponsor differed. Again, clinical signs and symptoms of acute respiratory infection. Radiographic change not related to another disease process or condition. The medical officer required that sputum samples and also endotracheal samples contain greater than 25 white cells and less than 10 epithelial cells per lower power field.

In neutropenic patients, the white blood cell count criterion was dropped, however, for all specimens, the epithelial cell criterion was used regardless of the type of specimens.

[Slide.]

In patients with either a blood culture which was positive or serological documentation, then, the last criterion discussed for sputum sample was dropped. The sponsor and the medical officer both used at least three full days of therapy, and five full days of therapy was used by the medical officer as a test of cure visit.

[Slide.]

To be found bacteriologically evaluable, the patient first had to be clinically evaluable, with a

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pathogen identified in either the respiratory tract or in a blood culture or serologically.

Two criteria used by the medical officer, and not by the sponsor, any culture that grew three or more organisms was found to be contaminated. However, in cases where there were quantitative cultures, if the pathogen grew at 10^4 cfu/ml or greater and the contaminants were listed as trace, then, up to three contaminants were allowed.

[Slide.]

This basically deals with prior antibiotics. Any systemic antibiotic for less than 24 hours was considered to be fine. If the pathogen responsible for the episode of pneumonia was resistant in vitro to the prior therapy, then, any length of prior therapy was allowed.

Lastly, in a situation where the patient received greater than three full days of prior therapy, a patient had to have clear documentation that the patient was not improving on this therapy to be found evaluable.

[Slide.]

Just a protocol note. For patients that had a pathogen growing which was resistant to either the study drug or to aztreonam, or to both in this case, then, the investigator could add either tobramycin or imipenem. In situations where pseudomonas was involved, both were

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commonly added and this was allowed for both arms.

[Slide.]

The number of clinically evaluable patients. For Synercid, 55 percent or 82 out of 150; for the comparator, 86 out of 148 or 58 percent.

[Slide.]

Reasons why unevaluable. The first three deal with the use of prohibited antibiotics, and they account for the vast majority of reasons why patients were found unevaluable.

[Slide.]

Fully evaluable patients, these being both bacteriologically and clinically evaluable, 37 percent in the Synercid arm or 55 patients; 44 percent in the comparator arm or 65 patients.

[Slide.]

Clinical efficacy rates were 54 percent as per the medical officer for Synercid, and 45 percent for the comparator as per the medical officer.

[Slide.]

For the fully evaluable patients, looking at the clinical response rate of patient level, which again is a primary efficacy analysis, the clinical cure rates were 60 percent for Synercid and 51 percent for the comparator, with

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the confidence interval as shown.

[Slide.]

Look at the full evaluable at a pathogen level, the stress here is on gram-positives. In patients who had a gram-negative infection, aztreonam was continued, and therefore, the stress here will be where Synercid can be compared to vancomycin. Staph aureus, 53 percent pathogen level eradication; vancomycin, 56 percent; Strep pneumo, 57 for 7 patients, and vancomycin, 4 out of 8.

Other gram-positives is really a whole mish-mash of all the streptococci. The total gram-positive, 52 percent and 60.

[Slide.]

For bacteremia patients, for Synercid--again, these are fully evaluable patients, looking at the pathogen level or eradication level--for Synercid, 3 out of 7 patients had eradication of Staph aureus from their blood, 43 percent; for the comparator, 4 out of 12 or 33 percent.

[Slide.]

Looking at MRSA, 21 patients were found clinically evaluable in the Synercid arm, and 18 in the comparator arm. For fully evaluable, 18 and 18. Twenty-four percent were clinically cured for Synercid, and 39 percent for the comparator, 5 out of 21, and 7 out of 18, similar numbers to

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those Dr. Talbot presented this morning.

For bacterial eradication, 6 out of 18 for Synercid, and 9 out of 18 for comparator. To look at these 12 failures and these 9 failures, for the 12 in the Synercid arm, 10 had persistence and 2 had presumed persistence; for the 9 failures here, 8 had persistence and the 1 had presumed persistence.

[Slide.]

As Dr. Marsik had mentioned in two talks prior, there is a concern that for Staph aureus with MLSB constitutive resistance, there could be a decreased activity of Synercid against these strains, so we tried to pull out the patients who had documented MLSB constitutive resistance against small numbers of patients, 12 and 10 for the two evaluable groups for Synercid, and 11 each in the comparator. It should be noted that the vast majority of these patients were also MRSA strains and the efficacy rates are as shown.

[Slide.]

Adverse events. There were 70 patients who died during the study, 25 percent of the Synercid patients and approximately 22 percent of the comparator. None of these were considered to be probably related to study drug.

As far as non-venous adverse events, 26 percent

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overall for Synercid, 6.1 for the comparator. The most commonly seen non-venous adverse events which appeared to be possibly or probably related to Synercid use were digestive system, skin, and muscular system, with numbers for the same three systems for the comparator arm.

[Slide.]

For venous adverse events, a total of 28 patients or 18.7 patients had a venous adverse event. Again, as Dr. Talbot mentioned, what is described here as a whole slew of conditions, be it redness, pain, irritation, phlebitis, et cetera, at the peripheral venous site.

For the comparator, 16 patients had such an adverse event, which comes out to approximately 10.7.

If you look at a denominator of patients who had a peripheral line, it is 20 out of 67, or 41.8 for Synercid; 16 out of 57 or 28.1 percent for the comparator.

Lastly, looking at discontinuations, 23 patients in the Synercid arm or 15.3 percent; for the comparator, 14 patients or 9.5 percent.

[Slide.]

I will torture you with one last slide. This is a summary slide of some issues that are raised by the HAP study. Evaluability, again, primary analysis done on a fully evaluable population, the range is fairly low at 37 to

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44 percent.

Efficacy rates were 51 percent for the comparator or for vancomycin, and 60 percent for Synercid. In all honesty, lower than expected cure rates for vancomycin at the 51 percent.

It was mentioned that the Points to Consider do stress that only one study is required for approval for hospital-acquired pneumonia, however, that is usually viewed in the light of other low respiratory tract infection results, just to keep this in mind when the community-acquired pneumonia study results are presented, and brings up the question are corroborative studies required.

Lastly, for MRSA, fairly low numbers of patients and efficacy rates were fairly low if the persistence rate is fairly high.

Dr. Susan Thompson will now present community-acquired pneumonia and complicated skin and skin structure infections.

Skin and Skin Structure Infections/

Community-Acquired Pneumonia Safety

DR. THOMPSON: Good morning.

[Slide.]

I am going to be presenting today the FDA analysis

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of two traditional indications, the first of which is community-acquire pneumonia.

[Slide.]

As you have already heard, the indication of community-acquired pneumonia had two studies submitted, JRV 302 and 303. They were both comparative studies, 302 was open-label, and 303 double-blinded. Again, as you have heard, the regimen was Synercid in the dose of 7.5 mg/kg q12 hours. The comparator regimen consisted of ceftriaxone in addition to erythromycin. As Dr. Talbot discussed earlier, one adjustment was allowed in the comparator arm of either ceftriaxone or erythro.

[Slide.]

Study 302 enrolled 494 patients at 74 study center in 7 non-U.S. countries. Study 303 enrolled 508 patients in 60 study centers in the United States.

[Slide.]

I am going to briefly run through some of the pertinent inclusion and exclusion criteria, as well as clinical evaluability criteria that we used, and try and highlight some of the differences that we did use with respect to the sponsor's.

Of course, patients were included who had clinical signs and symptoms of acute respiratory infection, as well

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as radiographic evidence of a new pulmonary infiltrate not related to another disease process.

We did require for a patient to be clinically evaluable that they have a lower respiratory tract specimen with a Gram stain demonstrating greater than 25 white cells and less than 10 epithelial cells per low power field. We did, however, make the following exceptions to that rule:

First of all, if serologic documentation of atypical pneumonia was present, this Gram stain was not required. That was also true if a causative pathogen was isolated by blood culture. Lastly, if the patient had a definitive clinical picture of acute pneumonia including, at a minimum, the presence of fever and lobar infiltrate, this Gram stain was not required.

[Slide.]

In order to be clinically evaluable, a patient could not have received systemic antibiotics prior to study initiation. The following exceptions, however, were made:

If less than 24 hours of systemic antibiotics had been received prior to study initiation; if the causative bacterial pathogen was demonstrated by entry culture to be resistant to study treatments; if the patient was deemed a clinical failure after receiving antibiotics for at least three days which were discontinued

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less than seven days prior to study drug initiation.

[Slide.]

In order for a patient to be regarded as bacteriologically evaluable, they had to be clinically evaluable, and a pathogen isolated from either the respiratory tract specimen or blood culture or detected serologically.

[Slide.]

Just to briefly highlight some of the differences that we had in terms of applying clinical evaluability criteria. I have already outlined to you the sputum Gram stain requirement that we did institute in order for a patient to be clinically evaluable.

We did require that fever be present at baseline for all patients who were enrolled as clinical failures of previous antibiotic therapy.

The third difference is that we did not allow a patient to be enrolled with a diagnosis of Legionella pneumonia with simply a single elevated IgG of greater than or equal to 1 to 256, but rather required the 4-fold in IgG or presence of IgM.

Lastly, we required that the test of cure visit occur between days 7 and 28.

[Slide.]

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Looking then at the set of patients who we did deem to be clinically evaluable, this slide divides it for you into the two studies, 302 and 303, and looks at the number of clinically evaluable patients by treatment arm.

You can see that in the Synercid arm, 124 of the 243 enrolled patients were clinically evaluable, or 51 percent. In Study 302, 53 were evaluable clinically in the comparator arm.

Looking at Study 303, 52 percent were clinically evaluable in the Synercid arm, and 57 percent in the comparator arm.

In this slide, you see broken down the reasons why patients were deemed to be clinically nonevaluable, in this case for Study 302.

The most common reason in both treatment arms was that there were insufficient signs and symptoms present at baseline, including either insufficient Gram stain criteria or just insufficient signs and symptoms that the patient presented with.

Additionally included in this category are patients who had incomplete data required for clinical efficacy analysis. Antibiotics given either prior or post-study additionally accounted for several other patients being nonevaluable, and I would like to point out in this

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slide that there is a fairly even distribution between treatment arms of reasons for nonevaluability.

[Slide.]

This looks at the same information for Study 303. Again, the most common reason for nonevaluability is the category of insufficient signs and symptoms.

[Slide.]

Looking then at those patients who were fully evaluable, that is, both clinically and bacteriologically evaluable, again divided between Studies 302 and 303. You can see that in the Synercid arm, 40 percent in 302 were evaluable, as were 41 percent in the comparator arm. Slightly lower numbers and percentages were fully evaluable in Study 303 with 29 percent in the Synercid arm, and 32 percent in the comparator arm.

[Slide.]

Turning to the clinical efficacy analysis of the clinically evaluable population at test of cure, which for this indication is the primary efficacy parameter.

We can see that in Study 302, by FDA's analysis, 69 percent of patients had a clinical success, 85 of 124, versus 84 percent of patients in the comparator arm, which was 111 patients out of 132. Given on the righthand side of the slide is the 95 percent confidence interval for this

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comparison.

For Study 303, the clinical efficacy rate was 68 percent in the Synercid arm, and 78 percent in the comparator arm, and again given on the slide is the 95 percent confidence interval. I will point out that this 95 percent confidence interval did not fall within the bounds that we required to establish equivalence between the two treatment arms.

[Slide.]

Looking then at the efficacy rates in the fully evaluable population, that is, in patients who were both clinically and bacteriologically evaluable, I have given here the bacteriologic eradication rates in the two studies.

You can see that in the Synercid arm, 69 percent had bacteriologic eradication of the pathogen present at presentation in comparison to 88 percent in the comparator arm.

In Study 303, you can see that 67 percent had bacteriologic eradication in the Synercid arm, and 83 percent in the comparator arm.

[Slide.]

This slide looks at the bacteriologic eradication again in the fully evaluable population in Study 302 divided by pathogen isolated either in blood culture or respiratory

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specimen or identified serologically at the time of presentation.

You can see that the two most common pathogens identified in these patients were Strep pneumoniae and Chlamydia pneumoniae, and given here are the bacteriologic eradication rates.

In the Synercid arm, 78 percent of Strep were eradicated in the Synercid arm as compared to 97 percent in the comparator arm. Seventy-six percent of Chlamydia were eliminated by Synercid, and 92 percent by the comparator.

I will point out that for the atypical pathogens that these organisms are presumptive eradications and based on the patients' clinical assessment since the diagnosis and followup was serological.

[Slide.]

This is the same information presented for you for Study 303. Again, Strep pneumoniae and Chlamydia pneumoniae were the most commonly isolated organisms with bacteriologic eradication rates of 77 percent in the Synercid arm and 87 percent in the comparator arm for Strep, for Chlamydia 68 percent and 77 percent.

[Slide.]

This slide outlines the results of bacteriologic eradication for patients who were bacteremic at initial

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presentation. Again, this encompasses the fully evaluable patient population.

I have given for you only Strep pneumoniae because other organisms were present in numbers too small to be significant.

In Study 302, 81 percent of patients, which is 13 out of 16 in the Synercid arm, had initial Strep pneumoniae eradicated, and 14 out of 14 in the comparator had this organism eradicated.

In Study 303, the percentages were 93 percent in the Synercid arm and 91 percent in the comparator arm.

[Slide.]

You have already heard a summary of the adverse events from these studies, but I would just like to briefly reiterate the adverse event profile seen in Studies 302 and 303 specifically.

This slide combines the results of the two studies, and includes 499 patients from the Synercid arm and 503 from the comparator arms.

You can see what were deemed the related by the investigator non-venous adverse events were less common in the Synercid arm, with 21 percent of patients experiencing an adverse event of that category in contrast to 31.8 percent in the comparator arm.

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Related venous adverse events were slightly more common in the Synercid arm with approximately 69 percent of patients experiencing this adverse event, as did 60 percent of the patients in the comparator arm.

You will notice that more patients in the Synercid arm had to have treatment discontinued due either to venous or non-venous adverse events. It was approximately three times more common in the Synercid arm for venous, and approximately twice more common in the non-venous adverse events.

[Slide.]

Just to briefly mention the deaths that occurred in these two studies. In Study 302, 18 deaths occurred, 12 in the Synercid arm and 6 in the comparator arm. There did not appear to be any trend or relationship in terms of association with either Synercid or comparator. One death in the comparator arm was deemed to be possibly related.

In Study 303, 6 deaths occurred in each arm of the study, and one in the Synercid arm was thought to be possibly related.

[Slide.]

Points to Consider then in consideration of the results of this study, the clinical evaluability rates ranged from 51 to 57 percent.

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Synercid demonstrated 69 percent and 68 percent clinical success rates at test of cure, while the comparator regimen had 84 percent and 78 percent success rates in the two studies. The 95 percent confidence interval analysis did not fall within the bounds required to establish equivalence between these two treatments.

The discontinuation rates due to adverse events were higher in the Synercid arm, as were the related venous adverse events. The related non-venous adverse events were higher in the comparator arm.

That concludes the presentation of the results of community-acquired pneumonia. There will be a short pause while we regroup and get the next group of slides.

[Slide.]

The last of the indications then that we are going to be presenting today is the FDA analysis of the complicated skin and skin structure infection studies.

[Slide.]

Again, two studies were submitted in support of this indication, entitled JRV 304 and 305, both of which were comparative, open-label studies.

Again, you have already heard about the regimens that were used, and both studies used Synercid in a dose of 7.5 mg/kg q12 hours. The comparator regimen did differ

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between the two studies with oxacillin used in Study 304 and cefazolin in 305.

You have heard that vancomycin could be substituted as the comparator regimen if methicillin-resistant organism was isolated or if the patient had a beta-lactam allergy, and this was of course in the comparator arm.

[Slide.]

Study 304 enrolled 450 patients at 43 study centers in the United States. Study 305 enrolled 443 patients at 89 study centers in 10 countries, which also included the U.S.

[Slide.]

Again, to just touch on some of the significant inclusion criteria, these patients were required for inclusion in the study to have an infection of sufficient severity to require hospitalization for at least 24 hours and to require parenteral antibiotics for at least three days.

The patients were also required to have an infection in which monotherapy with one of the study drugs was thought to be clinically appropriate. The protocol specified that patients were to be excluded if the skin and skin structure infections were likely to yield mixed

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pathogens, which was the phrasing of Study 304, or infections with pathogens presumed to be intrinsically resistant to Synercid or vancomycin prior to randomization.

[Slide.]

Inclusion criteria also required that a patient have a specimen available for culture and to have an infection of severity to require at least either a surgical intervention or to have the presence of an infectious process involving the deeper soft tissue layers.

[Slide.]

In order to outline for you the types of infections that were included in these studies, it was required that the clinical appearance be consistent with an infection predominantly due to aerobic gram-positive organisms.

These included infections following clear surgical procedures, erysipelas, which on review was usually a cellulitis, infection at central venous catheter insertion sites with the catheter being removed within 24 hours, severe carbunculosis, traumatic wound infections, and infections at foreign body sites, which again was to be removed within 24 hours.

[Slide.]

In order to be bacteriologically evaluable, the

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patients again had to be clinically evaluable, and at least one pretreatment gram-positive pathogen isolated. In addition, MICs had to be performed for that organism.

[Slide.]

Just to briefly highlight some differences between Protocols 304 and 305, which overall were very, very similar. Clean surgical procedures with entry into the GI, gynecologic, or respiratory tract were specifically excluded by Protocol 305, as were partial thickness burn wounds. There was no absolute requirement for the presence of drainage in Study 305. It was instead included in a list of signs and symptoms which should be present.

[Slide.]

To highlight for you briefly some differences in the evaluability criteria that we used in distinction to the sponsor, we did not allow the use of systemic antimicrobials during the study.

Patients who had study drug stopped due to an adverse event were classified by us as clinical failures. The test of cure visit by our evaluability criteria had to occur between days 7 and 30 after the completion of the study drug.

We did not accept Staph epidermidis as a causative pathogen except in the case of surgical site and catheter

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site infections.

Lastly, organisms with no MICs performed were rendered bacteriologically nonevaluable.

[Slide.]

Looking then at the set of patients who were deemed to be clinically evaluable, you can see in Study 304 that 105 out of 229 patients were clinically evaluable or 46 percent. In the comparator arm, 106 out 221 or 49 percent.

In Study 305, 51 percent of patients in the Synercid arm and 54 percent in the comparator arm were clinically evaluable.

[Slide.]

Looking at the reasons why patients were considered to be clinically nonevaluable, first of all, in Study 304, you can see that the most common reason was missing efficacy data. The majority of these patients were classified by the sponsor as nonevaluable due to this reason, and I concurred with this analysis.

The second most common reason was insufficient signs and symptoms at baseline. I would highlight for you the categories of incorrect diagnosis and infection types. These two categories include patients which were rendered nonevaluable because they had infections which were given in the protocol as to have been exclusions since specifically

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most of them were polymicrobial infections including other than aerobic gram-positives usually in patients with diabetic extremity infections or ischemic ulcerations.

[Slide.]

This is the same information given for Study 305 again. You can see that the most common reason for nonevaluability is missing efficacy data with smaller numbers of patients in other categories, and I would emphasize, as you did see on the previous slide, that there is a fairly even distribution of reasons for nonevaluability between the two treatment arms.

[Slide.]

Looking then at the patients who were considered to be clinically and bacteriologically evaluable, that is, fully evaluable, in Study 304, 27 percent of the patients in the Synercid arm fell in this category, as did 26 percent of the patients in the comparator arm.

In Study 305, the numbers were slightly lower, 21 percent in the Synercid arm and 24 percent in the comparator arm.

[Slide.]

This slide gives for you the clinical efficacy rates in those patients who were deemed to be clinically evaluable at the test of cure visit, which again is

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considered to be the primary efficacy parameter for this indication.

In Study 304, 52 of 105 patients had clinical success rates which was either cured or improved, or 50 percent. In the comparator arm, 55 out of 106, or 52 percent, in Study 304, had a clinical success.

You can see that the 95 percent confidence interval is given for you on the right.

In Study 305, 66 percent of patients in the Synercid arm were regarded as clinical successes, as were 64 percent in the comparator arm. Again, the 95 percent confidence interval is given for you on the right. These 95 percent confidence intervals do fall within the bounds required to establish equivalence.

[Slide.]

Turning to the efficacy rates in those patients considered to be fully evaluable, that is, that had a pathogen identified in addition to being clinically evaluable, the bacteriologic eradication rates are given for you here.

In Study 304, 47 percent of patients in the Synercid arm had eradication of their pathogen, as did 60 percent of the patients in the comparator arm.

In Study 305, 67 percent of patients in the

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Synercid arm and 55 percent in the comparator arm had eradication of their pathogens originally isolated.

[Slide.]

Looking at a breakdown of those organisms that were identified as the etiologic pathogen in the fully evaluable patient population, given here are the bacteriologic eradication rates, first in Study 304.

As one would expect, Staph aureus was the most common organism identified as the pathogen in these patients with complicated skin and skin structure infections.

You can see that in Study 304, 49 percent of patients in the Synercid arm and 63 of patients in the comparator arm had eradication of this organism.

Smaller numbers of organisms were present, as you can see, fairly even distributed between arms. Strep agalactiae, I would point out is one of the requested organisms, had zero percent success by our analysis, and 7 out of 8 or 88 percent in the comparator arm.

[Slide.]

In Study 305, again Staph aureus is the most common organism isolated, and the bacteriologic eradication rate in the fully evaluable patient population was 65 percent in the Synercid arm and 51 percent in the comparator arm, again from Study 305.

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Smaller numbers of organisms--other sorts of organisms I should say--in this case, we have Strep pyogenes that did have 100 percent eradication rate in the Synercid arm and 3 out of 8, which of course, is 38 percent in the comparator arm.

[Slide.]

I would just like to very briefly show you the eradication rate of methicillin-resistant Staph aureus in these studies. The abbreviations that you will see here are a little different than what I have used previously. The QD is, of course, Synercid, and C is the comparator arm.

Looking at the bacteriologic eradication of the MRSA, in those patients who were considered to be evaluable, you can see that relatively small numbers are present, but 56 percent were eradicated in the Synercid arm and 50 percent in the comparator arm, so quite similar numbers.

[Slide.]

Just to give you a look at again the bacteriologic eradication of Staph aureus with the MLSB constitutive resistance, again, very small numbers, but 50 percent in the Synercid arm and 50 percent in the comparator arm.

[Slide.]

Again, I would just briefly like to present to you the adverse events profile for these two studies. This is

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Study 304 and 305 combined. 450 patients were in the two studies in the Synercid arm, and 443 in the comparator arm.

In these two studies, the related non-venous adverse events were somewhat more common. In the Synercid arm, 24.6 percent versus 13 percent. This is also true of the serious non-venous adverse events.

The related venous adverse events were 68 percent in the Synercid arm and 33 percent in the comparator arm.

Again, discontinuations due to either venous adverse events or non-venous adverse events were more commonly found in the Synercid arm, 12 percent versus 2 percent, in the non-venous, approximately 12 percent versus 4 percent.

[Slide.]

Just again to mention to you deaths, which as one would expect in these complicated skin and skin structure infection studies were quite uncommon, 7 patients died in Study 304, all thought to be unrelated to study medication, and in Study 305, there were 4 deaths, again all considered to be unrelated.

[Slide.]

In summary, the clinical evaluability rates for these studies ranged from 46 to 54 percent. The results that I have presented to you demonstrate that Synercid had a

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50 percent and 66 percent clinical success rate in the two studies at test of cure, while the comparator regimen had 52 percent and 64 percent success rates.

The 95 percent confidence interval approach demonstrates equivalence of the two treatment arms.

The adverse events were higher in the Synercid arm, as were study discontinuations due to adverse events.

Thank you for your attention. That concludes the FDA presentation.

DR. RELLER: Are there any questions for the FDA presenters?

If not, we will have our lunch break. There is but one scheduled presentation at the open session, so that we will have some opportunity to close the time gap there. As a consequence, we will have the full hour and a half for lunch and reconvene promptly at 2:00 p.m., please.

[Whereupon, at 12:30 p.m., the proceedings were recessed, to be resumed at 2:00 p.m.]

AFTERNOON PROCEEDINGS

[2:00 p.m.]

DR. RELLER: We will reconvene.

Open Public Hearing

DR. RELLER: We now will have our open public hearing. Is Mr. Joe Turner here?

[No response.]

DR. RELLER: We had three potential persons speaking at the open public hearing, and it seems that none of those individuals is present.

That being the case, we will move to committee discussion, questions, and vote.

Committee Discussion, Questions, Vote

DR. RELLER: As presented this morning, the sponsor has requested through the NDAs 50-747 and 748 a wide range of indications for quinupristin and dalfopristin.

To help the agency in their decision about the specific requests presented, the committee has been asked to review four questions that have to do with interpretation of the data and whether or not we would recommend approval for the specific indications.

Now, we would like to have an open committee discussion of all members of the committee, voting and non-voting, and then we will ask those empowered to vote to

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forward our recommendations on to the committee.

The four questions are before you. We will go in order.

The first one: skin and skin structure infections. There are two parts to each of these questions.

The first part: Do Studies 304 and 305 provide evidence that Synercid is safe and effective for the treatment of complicated skin and skin structure infections? We were asked specifically in the discussion to consider the overall efficacy rates in the two studies.

Overarching the discussions are issues that have been pointed out both by sponsor, as well as the agency, that there are unusual considerations in many aspects for what we have been presented and we have fortunately a good amount of time to have a full and complete discussion of all of the issues.

Who wishes to start?

DR. SOPER: I will jump in.

DR. RELLER: Dr. Soper.

DR. SOPER: Is anybody concerned about the rather poor proportion of patients that are evaluable? The going rate here seems to be less than 50 percent which, when stratified in some cases, even goes down to 20 percent, and it just seems to me that we are throwing an awful lot of

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patients out of the evaluation process.

DR. RELER: Dr. Norden.

DR. NORDEN: I am concerned about it also, but one of the things I did notice, particularly in the FDA analysis, is an intent to treat analysis, and I wondered if that is left out and why it is left out, I guess.

DR. ROBERTS: We did attempt to perform an intent to treat analysis, and the sponsor actually in their package did present an intent to treat analysis. I think Dr. Talbot presented one mention of an intent to treat analysis.

The problem was there was a number of patients for which they were called indeterminate with respect to a response, and those patients were not apparently followed out enough to give a response. So, all those patients essentially became essentially failures because they went into the denominator.

So, when recognizing this, we decided that we could not really do a true intent to treat analysis. So, ours would simply be very similar to that of the sponsor's. Obviously, if you put the indeterminates in the denominator, the overall efficacy rates for both sides were lower than the intent to treat analysis, if you took them out, then, they were still somewhat lower, but again consistent with that of the evaluable population.

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DR. RELLER: Dr. Archer.

DR. ARCHER: I guess I would like some sense of what kinds of infections, particularly the Staph aureus infections were. An efficacy rate of the comparator, you know, oxacillin of only 60 percent against a methicillin-susceptible Staph aureus infection is a little low, if it were truly just cellulitis or even a deeper infection.

Could you give me some sense of what kinds of infections these were?

DR. THOMPSON: I can answer that or certainly Dr. Talbot can address that also.

DR. TALBOT: May I answer, Mr. Chairman, to the first point made?

DR. RELLER: Sure.

DR. TALBOT: The question was about the number of evaluable patients in these skin studies, for example, and we took the approach that we have seen used in the past, which was that for evaluation of anti-infective drug products, the approach is to try to distill the population examined in the trials--could you put the lights up a little bit for us, please--to distill a population in which a treatment effect can truly be ascertained, that is, to apply rigid both clinical and bacteriologic evaluability criteria

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to try to get to that population which truly tells you something.

So, that is an approach we took, and it is one that our colleagues at FDA took. Now, as an ex-clinician, I also happen to agree with Dr. Norden that the all-treated population is one that is very important because physicians treat patients as an all-treated population, and not as an evaluable population.

So, we did place emphasis in our analyses on the all-treated populations. I do agree with the comment made by our colleague from FDA that the presence of indeterminates has to be considered, but we did take the conservative approach of assuming that they were failures.

[Slide.]

Now, if you look on the screen--perhaps at this point we will need the lights down a little bit--this slide shows for the complicated skin and skin structure infection indication, the clinical success rate in both the all-treated and the clinically evaluable populations with the all-treated populations shown here and the clinically evaluable populations shown here.

So, you have seen these numbers before as presented during my primary presentation. If you look above, you see, as Dr. Roberts mentioned, that in the

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all-treated analysis with the indeterminates considered as failures, that the response rates are lower. They do remain comparable in each group.

The point estimates of the difference in response rates remain low, and the confidence intervals are really relatively symmetric and certainly fall within a range that would be considered to demonstrate equivalence by the usual standards, which arguably might not be appropriate to apply here, but at least for your guidance are provided.

So, we would suggest that the all-treated analysis is important and, in fact, does confirm the results of the primary analysis, namely, clinical response in the clinically evaluable population.

DR. ARCHER: Could you comment on the second question?

DR. TALBOT: I am sorry. The second question?

DR. ARCHER: What kinds of infections are we talking about here, particularly the Staph aureus infections?

DR. TALBOT: If you will give us a second to pull the slide out, I can show you that.

[Slide.]

This slide shows by study the distribution of presenting conditions in the two studies.

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DR. ARCHER: Do you have this broken down by organism?

DR. TALBOT: No.

DR. ARCHER: Because one would not think that erysipelas is caused by Staph aureus very often.

DR. TALBOT: Agreed. Yes.

DR. ARCHER: And yet I don't see any group A strep down here on the list--well, a couple, 10, I am sorry.

DR. TALBOT: There were some group A strep, as I recall.

DR. ARCHER: There were some, yes, I am sorry. Most of the Staph aureus, then, were wound infections one would assume?

DR. TALBOT: They would be wound infections, clean surgical wound infection, carbunculosiis, CVC infection.

I think the message we take from this slide is that there is a distribution of different types of infection which should improve generalizability, and there also seems to be balanced between the two study arms.

DR. ARCHER: Do you have any data on which of these kinds of infections failed therapy, either for the comparator or for Synercid, because about 40 percent, if you look at both studies, failed Staph aureus infections.

DR. TALBOT: Offhand, I can't tell you that.

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Again, if you will give me a second to look for a backup slide, we will do that.

[Slide.]

We did perform logistic regression analyses to attempt to determine variables which would be independently associated with response. I am not going to take you through all of this, but just to show you for Studies 304 and 305--which we pooled because the results were similar--we looked at clinically and bacteriologically evaluable patients, and looked at outcome for clinically evaluable patients, that is, the primary efficacy parameter.

I think that the point here is that we examined a number of different variables that you can see listed here including the variable of erysipelas, since it was the most frequent indication, and attempted to examine, as I said, whether there were any specific variables associated with response.

[Slide.]

So, examining clinical response in the clinically evaluable population, the following findings were demonstrated. Diabetes was associated with failure, as was peripheral vascular disease and obesity, certainly things that would be clinically reasonable. Requirement for surgery also. There was association with enrollment in

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France, and an interaction of Synercid and age.

So, I think, to answer your question, erysipelas and underlying conditions did not show up in this analysis.

DR. RELLER: Dr. Judson.

DR. JUDSON: When I first came onto this committee, I think about five years ago, I was forced to confront what I had sensed clinically for a number of years, and that is that this whole category of skin and soft tissue structure infections is just problematic, and I think the sponsor has probably done as good a job as most of the others that I have reviewed here over those years, the problem being that this category is so heterogeneous that it runs a range from relatively minor infections which would get better without antimicrobial agents at all, through to life-threatening infections, such as extensive erysipelas, which will kill you even if you get the appropriate antibiotics.

Many times the isolates that we obtain are still not really the cause of the cause of the infection or the condition that we are treating. Therefore, I don't think, with the size of sample, when you get down to subsets or cells, that you have an adequate residual sample to even begin to compare the outcomes with any reasonable power, so we are stuck there.

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I was noticing that severe erysipelas, if I understood this correctly, or one category was greater than 25 square centimeters--is that correct-- which gets down to 5 by 5 cm, which means 2 inches by 2 inches, and that is not a very--if I am interpreting that properly--that is not a very large area of erysipelas.

But any rate, it just simply speaks to the overall difficulty in coming to a reasonable interpretation. I don't know the answer. I have always wished we didn't have to review skin and soft structure studies.

DR. TALBOT: Well, if you would like to move on to another category, that would be fine with us, but seriously, to try to answer that question, yes, there are methodologic difficulties. I think, though, that there are some advantages to studying the infection in this way. For example, the generalizability to the clinical setting is probably greater. Clinicians treat many different types of infections.

We have two studies with relatively large numbers of patients, which by both our analysis and the FDA's analysis, show the same results. What I would like to emphasize in terms of trying to reassure you perhaps a little bit about the types of patients here is this was complicated skin and skin structure infection, so there was

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an attempt to add enrollment made and also in terms of evaluability, to assure that the severity of the infectious process was substantial. I think we are about to have a slide to show that.

[Slide.]

So, we examined in these studies complicated skin and skin structure infections predominantly due to aerobic gram-positive organisms including infections of clean surgical procedures and traumatic wounds, which gives you an idea of what was enrolled--who was enrolled, excuse me.

The infectious process had to be suspected or confirmed to involve deeper soft tissues including fascia and/or muscle layers. The erysipelas was allowed if the infection was deemed to be of sufficient severity to warrant parenteral antibiotic therapy.

So, I would still grant your point that some of these infections in certain patients could be heterogeneous, but I would also like to reassure you that there was an attempt to comply with the spirit of the complicated skin and skin structure infection indication as defined by FDA.

DR. JUDSON: I am not questioning at all your efforts in that regard. It is just a tough area.

DR. RELLER: Dr. Norden.

DR. NORDEN: It seems to me that in some ways, by

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strict criteria, this is the easiest question to answer. I mean the sponsor evaluated--or there were 218 evaluable patients in the Synercid arm, was also equivalent to the comparator agent. I think to worry about the absolute success rate is not valid given that you can't really compare from the study done with drug X to drug Y, and so on.

My concern probably is not to do with this direct indication, but this is not the area where I think most of us, as clinicians, would want to use Synercid unless we are dealing with MRSA, because we have lots of other drugs at the present time. So, that is not a reason not to approve it or not to recommend approval. I think on the strict criteria, the sponsor has met the standard that is required for this indication.

DR. RELLER: Dr. Parsonnet.

DR. PARSONNET: I just had a question for the FDA. This gets back to Dr. Soper's question in the beginning about the number of evaluables.

What sort of clinical difference, given that you lost a lot of subjects to become evaluable, what was the clinical benefit that you would have been able to observe given the power of the sample size?

DR. THOMPSON: I am not sure quite how to answer

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that question, but let me just back up and say that the majority of the difference between the evaluable patient set that we had, and that the sponsor had, were the elimination of patients from our evaluable set who had infections that wouldn't a priori be expected to respond to Synercid, and in particular there were patients were polymicrobial infections of the lower extremities that at baseline had gram-negatives and anaerobes, or that would be predicted to have those based on the patient profile.

DR. PARSONNET: That is not really my question. My question is what is the difference you would have been able to detect in the study given the number of subjects in the study. You have about 200 some-odd evaluables in the two groups. I want to know what difference between the two of them you would have been able to detect.

DR. THOMPSON: Actually, I don't have that information off the top of my head.

DR. LIN: Daphne Lin. We do not have computer power, you know, for this case here. I think you have got a very good point. For this case here, for example, Study 304, we have clinical evaluable only in 105 patients in Synercid for Study 304, and the comparator, only 106.

Originally, when sponsor computer the sample size, I think it was based on the pure rate is much higher.

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Unfortunately, we do not have computer power, but your right.

DR. SOPER: If your slide is correct, the clinical and bacteriologically evaluability in this study in 304 was 27 percent and was 21 percent. That means 70-plus percent of the patients that were enrolled in this study were excluded for some reason.

DR. THOMPSON: Just to be clear, that particular slide refers to those patients that are both bacteriologically and clinically evaluable, which in this study is actually not the primary endpoint, but that is a true statement.

DR. TALBOT: Just to emphasize that, that FDA Points to Consider document clearly states that clinical response in the clinically evaluable population is the primary efficacy parameter, and in thinking about that, we believe that that is a good choice.

That is not just because of the results of the studies, but just speaking clinically, for patients with skin infections, we all know that it can be difficult to identify pathogen at baseline, whereas, it is really quite easy to make a clinical diagnosis most of the time, and it is also relatively easy to assess a clinical response, but assessing a bacteriologic response is confounded by the fact

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that sampling of an infection site after it is, for example, partially healed, can leave you with colonizing organisms as opposed to pathogenic ones.

So, really, the clinical response in the clinically evaluable population seems to be the relevant parameter. Also, I would mention that I think the numbers you are quoting are the numbers from FDA, our numbers were higher, and I would like to just note again that we pursued a rigorous analysis and we did utilize an external steering committee blinded to treatment group for assessment of outcome or evaluability in situations where there was some question.

DR. RELLER: Dr. Chesney.

DR. CHESNEY: At least in pediatrics--and I realize you don't have many children--but I assume this is true for teenagers and young adults also, streptococcal infections are a major concern when we talk about skin infections, and I wonder if you have very much information with respect to necrotizing fasciitis, which is certainly the most severe streptococcal infection.

I think if this were on the market for skin infections, people would assume that it was effective for severe streptococcal cellulitis and necrotizing fasciitis, and with the small numbers of streptococcal infections we

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have here, I wondered if you had any additional information about the very severe forms.

DR. TALBOT: Several points there. First of all, we studied this agent in adults, so we could only draw conclusions about efficacy in adults. Second of all, patients with severe necrotizing fasciitis were not included, the type of flesh-eating bacterium that occasionally make it into the newspaper, so we could not extrapolate to that setting, as well.

We do efficacy on, as you pointed out, smaller numbers of Strep pyogenes, and those results by both our analysis and I think the FDA would agree by theirs, appear good, but ultimately, I think that--perhaps my regulatory colleagues or FDA would want to clarify--but this is the sort of thing that could be addressed in labeling, that is, any particular subsets for which there might need to be particular information given.

So, overall, as Dr. Norden has mentioned, equivalence was shown in an FDA indication, defined indication, in two studies for the primary efficacy parameter. We could address certainly any caveats within the labeling.

DR. RELLER: Dr. Chesney.

DR. CHESNEY: I think I understand even though I

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am new here, the issue of equivalence, and necrotizing fasciitis does present just like a cellulitis, so I think to say, to put a caveat that it might not cover necrotizing fasciitis, probably people wouldn't read that, and their initial impression always is that it is a cellulitis.

DR. TALBOT: Well, I am not saying that it would not cover necrotizing fasciitis. I am saying only that it has not been studied there and I tend to be data driven.

As you know also, necrotizing fasciitis is a very aggressive disease, and in fact, failure may not be antibiotic related. Even with the most active antibiotics available--and penicillin, when the bug is susceptible, the antibiotic of choice, the disease may progress in an unremitting fashion when a group A strep, a virulent group A strep is at fault requiring amputation.

So, I think in my view, those two things are a little bit too unrelated, and we certainly wouldn't want to generalize to situations that haven't been studied.

DR. RELLER: Dr. Christie.

DR. CHRISTIE: Although equivalence was demonstrated, the overall success rate was lower than you would have expected with other antimicrobials. Would that make a difference with regards to whether or not this would be recommended for this indication?

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DR. RELLER: We had in the trials presented a comparator agent. I think one of the issues that has been brought up with the number of evaluable patients is whether there is anything different about the patients in toto, both in the comparator, and well as in the Synercid arms that raises concern among the committee.

DR. CHIKAMI: Dr. Reller, may I make a comment on that?

DR. RELLER: Yes.

DR. CHIKAMI: I think, as Dr. Norden pointed out, it is often difficult to generalize across randomized controlled trials in terms of comparing absolute response rates. That is one of the reasons why in the regulations, there is the requirement for adequate and well-controlled studies in which to compare the test agent or investigational agent to either placebo control or, in most cases, with antimicrobial agents we use active controls.

Over the years, the Division has developed Points to Consider in terms of assessing this idea of equivalence in terms of drawing the inference that if the test agent is equivalent to an agent which we consider to be an active comparator and approved product, that then we would make the inference that the test drug is active for the infection being treated.

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So, I understand your point, but I think again we need to analyze the data in the setting of the randomized controlled trial that has been conducted for the test agent.

DR. TALBOT: May I comment, Dr. Reller?

DR. RELER: Dr. Talbot, please.

DR. TALBOT: Just a brief comment. I appreciate the comment from Dr. Chikami.

I think the point here or there are two points here. First of all, we in essence did an extra trial. The FDA Points to Consider suggested one would be adequate when associated with pharmacokinetic data on skin penetration, but as our colleagues have mentioned, they asked us to do another one because we were pursuing just a few indications, and so we did that.

So, we took an extra there. The other point is that remember the comparators were different in each of the two studies, so we have an external anchor that is different in each of the two studies, and it suggests that the absolute level of response is absolutely only in these studies. It is driven perhaps by the evaluability criteria that were applied by us and by FDA.

When we put the package together, we think we have two studies, two different comparators, equivalence in each, and that provides a great deal of certainty about the

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results.

DR. RELLER: Before we vote on these questions, we want to make sure that we look at all aspects while there is an opportunity. Ultimately, in any approved drug for a given indication, there is a listing of the category in accord with the Points to Consider, as well as owing to, and a listing of pathogens.

Some of the questions that have been raised have to do with whether the body of infections presented is representative of what is seen in skin and skin structure infections, and the other has to do with the distribution of organisms and how this compound might be used.

There are two parts to our question. One is the safety and efficacy based on the data presented. The second part, that is clearly closely related, but not necessarily exactly the same, is whether or not the committee recommends approval recognizing that it is not us, but the agency that approves these drugs.

With those points, is there any additional discussion that we want to undertake before calling the question? Yes.

DR. ARCHER: I guess it is reasonable to bring it up now. I realize the company is not asking for an indication for Staph aureus bacteremia, but it does occur

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with skin, and there were not enough to really evaluate in this study. But I am very concerned about the MSLB constitutive resistance in a patient with Staph aureus bacteremia for which I think there is ample evidence that without the streptogramin B component, this is basically a bacteriostatic drug.

I am concerned that patients with potential bacteremia, possibly endocarditis, possibly seeding, will get treated with a bacteriostatic drug is this is methicillin-resistant, MSLB constitutive, and I wondered if there is any way to address that.

I don't think that the data the sponsor submitted has allayed at least my concerns about the lack of bactericidal activity in this situation.

DR. RELLER: Dr. Nadler.

DR. NADLER: I would ask the chairman if we be allowed to further elaborate on the rat endocarditis model.

DR. RELLER: I am not sure how persuasive that is even. For one thing, I think the rat endocarditis model is an okay model, I don't think it is as good as some other models of endocarditis, and there is also the issue of relapse when a bacteriostatic drug is used to treat endocarditis and which the animal models don't address. That is, therapy is not stopped, and the animals are not

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allowed to relapse in general. I think that is a major concern. There is not enough clinical data on treating endocarditis or prolonged bacteremia in patients with Staph aureus with the MLSB constitutive phenotype in order to make recommendations for or to allay fears about whether or not this compound will be effective.

Dr. Nadler, did you want to say something?

DR. NADLER: I just wanted to see if the committee wished to have further information on what is now the present rat endocarditis model with the modified dosing, et cetera, because it is our perspective that in the rat endocarditis model, we can demonstrate with the proper dosing bactericidal activity.

It is also our peers' perspective that the presence of the MLSBC-resistant phenotype is not enough demonstration of the absence of bactericidal activity. As I had said this morning, our knowledge of the impact of the MLSB-resistant phenotype has evolved with time and even subsequent to the filing of the dossier, we continue to aggressively look at that question.

So, I do think the animal model from an in vitro perspective allows us to look--or a microbiological perspective--look at what we see, and that is, bactericidal activity appearing when the animals are properly dosed.

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I have asked my clinical colleagues to see if we do have data in the human trials regarding MRSA and septicemia, and we are looking for that right now.

DR. MURRAY: I might just throw in a question at the same time, and that is, is bactericidal activity a criterion for approval for skin and soft tissue infections, and I don't know what are approved drugs. I know what we use, but there are certainly some drugs that are not bactericidal, that are used with some frequency for skin and soft tissue infections.

DR. ARCHER: I agree with that. My concern is bacteremia, and bacteremia does result not infrequently from a serious Staph aureus skin and soft tissue infection. I am concerned if it's not efficacious, patients may be rendered a disservice.

DR. RELLER: Dr. Lumpkin.

DR. LUMPKIN: Thanks, Dr. Reller. One area that I think would be very helpful to us to have some committee discussion on as you ponder this question, as you pointed out, this is not just a question of efficacy. This is a risk-benefit decision that we need to make, and we need your advice.

Separating this from the VREF that we will get to later, you know, when we looked at this, we are talking

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about an indication that is a standard indication for the most part compared against a routine series of antimicrobials, and people have talked about the equivalence of the efficacy side, but I haven't heard any discussion on the safety side.

I think when we looked at the adverse event profile of this product versus the comparators, particularly looking at discontinuations due to venous irritation and these other issues, one of the things that would be helpful, I think, would be are these issues that the committee feel are things we need to take into consideration when we make our decision or are the kinds of safety events that were shown in the clinical trials, ones that the committee is willing to accept given the kinds of infections that are being treated here.

DR. RELLER: Dr. Chesney.

DR. CHESNEY: I think that is a very good point. I wasn't going to comment so much on that, but my concern is if this is approved for skin and soft tissue infections, and gets very wide use, will we create a population of organisms that make it difficult to use for vancomycin-resistant enterococcus faecium.

I am concerned that it might be better to reserve it for a very important population rather than disseminating

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it widely and creating an increasing resistance population, which is a slightly different issue than Dr. Lumpkin was addressing.

DR. RELLER: Dr. Talbot.

DR. TALBOT: You have raised three very interesting issues. The first one relates to the issue of the requirement for bactericidal activity in treatment of complicated skin and skin structure infection situations, and I would have to agree with Dr. Murray that it is not at all clear that that is necessary for this indication.

DR. ARCHER: Once again, that is not my point.

DR. TALBOT: Well, we were talking about skin and skin structure infection, so I am just trying to respond to the point made. I understand your concern, Dr. Archer, and we may wish to discuss within a different context. I think it is a very valid question, but Dr. Reller had been asking us to speak about skin. So, I think we would maintain again that given the many different agents used for treatment of skin infection of this type, that Synercid would compare favorably based on the data shown, and I can show you the bacteremia data for each indication in a moment.

Now, with regard to the safety profile, we have tried to be very transparent with you about what the safety considerations are, and those of course would be reflected

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in labeling, so for a clinician using the drug in practice, it might be that in fact the most appropriate use would be patients with complicated skin and skin structure infection, hospitalized, of course, who would not have a problem with venous tolerability, who already had a central line, for example.

If that information about the safety profile is provided in labeling, then the clinician can make the appropriate judgment at that point.

With regard to the last point made over here about the issue of what the use should be given a public health question of VREF, that is a regulatory, as well as a philosophical issue that we could certainly talk about at length, and is one that is worthy of discussion indeed, but I think here the question is whether safety and efficacy have been shown in this indication.

I think if I understand the question posed to Dr. Reller and to the committee, that is the question that should be answered here. So, if you would like me to show you the data in bacteremia, I can do that, Dr. Reller.

DR. RAKOWSKY: Dr. Reller, if I can answer Dr. Chesney's question. We had an advisory committee in July of '96 where we specifically addressed the topic of such a drug development plan, and the general feel that was obtained at

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that advisory committee meeting was that too restrictive a label would actually stunt the development of drug in the pipeline where companies would be almost afraid to pursue a resistance indication if they were not allowed to get the more traditional indications with a larger population involved.

Even though it is a very important practice of medicine issue, from a regulatory viewpoint we have taken the stance that it is something which did not fall from the realm of what we would put in the label.

DR. RELER: Does anyone on the committee wish to have further data presented by Dr. Talbot to help in their decision when we come to voting?

DR. PARSONNET: I am still concerned about the power of the study to detect differences between groups, and I guess since you are asking efficacy and safety, it is very hard for me to know whether the drugs are comparable, whether the two arms are comparable unless we have a sense that there were enough people studies to actually evaluate that.

So, I am wondering if somebody could provide me with some sense of what samples, how these sample sizes match with what you really would have needed to have to be able to detect differences.

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DR. TALBOT: Dr. Ray Zhu, who is our statistician, can comment on that. Before he does, I will just mention that the guidelines call for one study. We have two studies, two entirely different sets of patients, two different geographic locations, two different comparators, so there is interstudy consistency, which I think has to be incorporated into the discussion.

Dr. Zhu.

DR. ZHU: Ray Zhu, statistician from RPR.

Regarding power time computation, when we did the computation, we tried to have enough power, so we reduced the so-called statistically type 2 error, which is when two treatment or comparator are actually equivalent, but we fail to show the equivalence, but in this case of two skin or skin structure studies, both studies actually showed equivalence.

Here, I think the power is not a concern anymore. I think the other error, which is type 1 error, when you don't have equivalence, but you happen to show it, that has been incorporated into the statistical testing procedure as indicated by Points to Consider controlled it per study within 2.5 percent.

So, by two studies actually that is 2.5 percent squared. So, we don't have a chance to make type 1 error.

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DR. RELLER: Dr. Savarese.

DR. SAVARESE: Yes. Jack Savarese, RPR. I would like to echo Dr. Rakowsky's comments regarding concerns about drug development.

Clearly, all of the caveats that have been mentioned here are obviously very valid of concern. Many of them can be addressed with the agency as the label is being finalized, however, given that the FDA has provided guidance on what constitutes an approvable indication, a sponsor goes about then attempting to comply with those guidances given all the caveats, and once the sponsor has, in fact, complied with that, then, for there to be a reconsideration of whether or not indications should be approved, makes it a very difficult situation in the pharmaceutical development area and also for the Food and Drug Administration.

So, I think we must keep in mind that we could probably spend hours raising many, many caveats about this, but there is a history, two drugs being developed, drugs are developed this way, FDA has evolved guidelines based on precedent, how other drugs have been approved.

This is not much different for a fairly standard indication. In fact, it has gone beyond what is required, two, adequate, well-controlled trials demonstrating

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equivalence. So, to turn away from that because of many other concerns presents a real problem, I think, for all of us.

That is a consideration that we have to face, that we are working within perhaps some constraints of having to set certain criteria, but we set those criteria, try to keep the playing field level for the development of all anti-infectives, and take the step that needs to be taken to approve those new anti-infectives for those particular indications.

We know that your job is very difficult given all of the concerns, but given the bottom line and the big picture of how this all works, we feel that demonstration of equivalence has been shown and the next step would be for there to be the committee's agreement with that.

DR. RELLER: We want to have a complete discussion and I think we are getting all the issues out on the table and focusing on this question, the primacy of efficacy and safety being the determinates, but a part of that is whether people on this committee are comfortable with the data having to do with efficacy and we want to make sure that if there are any responses regarding differences in safety of these compounds, that we get them out before we vote.

Dr. Parsonnet, do you have your question answered

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or not?

DR. PARSONNET: I just wanted to ask one more question of the statistician, which relates to when you talked about your error and whether that was related to the evaluable patients or whether that was related to the total population you initially selected.

DR. ZHU: Yes, actually, it applies to both evaluable and total patient, the compounds.

DR. RELLER: The criteria for efficacy are quite clearly outlined in the Points to Consider. The clarity of what is required for safety is more of a judgment call. Risk-benefit, number of options available that will certainly be a part more so of some of the other later discussions perhaps than with this one.

Any comments from the committee or issues in that light that you wish to bring up about safety? Carl.

DR. NORDEN: I guess I relooked at this, and I am taken by Dr. Lumpkin's question and comment, and I want to be sure that, Susan, the numbers that you gave us in safety study, in one of your last slides, discontinued secondary to venous adverse events 12 percent, discontinued secondary to non-venous adverse events 11.8 percent. Are any of those the same patients, or is this really 24 percent of patients discontinued therapy on the Synercid arm in these two

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studies?

DR. THOMPSON: My recollection is that that is the primary reason for discontinuation of patients.

DR. NORDEN: I think that is something we have to ask about in our thinking. That is a lot of people, 1 out of 4 basically who stopped therapy, if I am correct.

DR. TALBOT: Would it help the committee to actually examine in more detail the adverse events seen in these two studies?

DR. NORDEN: It would help me, yes.

DR. RELLER: Please. This is why this question has been raised. We need to look at these fully.

DR. TALBOT: While we are putting this up, I think you elucidated the question about safety very well. For any given patient in terms of prescribing, I think as Dr. Gilbert emphasized, the first question is efficacy. As you understand by now, we feel we have demonstrated efficacy.

With regard to safety, that is obviously critical for the prescribing physician to understand, so that the safety profile can be matched to a particular patient, but the safety profile is, as you all know, very, very well described in the labeling. This will not be a secret. So, a given physician can balance the known efficacy of the drug with the safety profile as related to his or her patient.

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[Slide.]

These are the most frequently reported adverse non-venous events related to study medication in the two skin and skin structure infection studies pooled. You can see the total number of patients here, and patients with related adverse events 25.1 versus 13.1, and going through the list here you can see that there were--let me get the paper copy since I am at a disadvantage--for body as a whole, the rate was 8 percent for Synercid versus 3.8 for comparator.

Some of those patients had what was defined as pain, which we can't be sure in each individual one of these, it may have been arthralgia and myalgia. Cardiovascular system 1.1 versus 0.5. Digestive system was a major contributor to this 10.7 versus 5, with diarrhea, nausea, and vomiting being noted in the Synercid group. So, those are events which certainly are of concern to the patient, but are not life-threatening and are reversible upon discontinuation of treatment.

[Slide.]

Just continuing through the list, metabolic and nutritional disorders, which could have been things such as hyperglycemia, for example, 1.1 versus 0.2, musculoskeletal 3 cases, which may have been arthralgia/myalgia, nervous

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system is quite balanced, respiratory system very few, and then the other major contributor was skin and appendages, pruritus and rash.

So, we are talking about the sorts of adverse events, namely those in the digestive system and the skin and appendages system, which can be seen with many types of antimicrobial agents available today.

DR. NORDEN: George, I am sorry, that doesn't really address the question of what reactions cause--again, maybe the FDA has it--but you still have 24 percent of individuals discontinuing Synercid therapy.

DR. TALBOT: I am sorry if I didn't answer your question. Some of those related adverse events led to discontinuation. The other factor was discontinuation due to adverse venous events.

DR. NORDEN: Right, but some of those, though, it still looks to me as though 23.9 percent.

DR. TALBOT: For adverse venous events, the percentage was about 11 percent, which is related to the peripheral venous intolerability of the drug, and as I mentioned previously, that may dictate how a physician in practice would use the drug, understanding that this is a problem. Having it reflected in labeling will allow a physician to make a decision as to whether this is

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appropriate for use in a patient without a central venous catheter.

In terms of other events leading to discontinuation, the digestive system, adverse events led to discontinuation in 2.4 percent as compared to 0.2 percent for comparator. Those comparators, remember being oxacillin and cefazolin, are relatively well tolerated in the GI tract, and perhaps if we had used different comparators, some of the macrolides, the rate of digestive system adverse events might have been higher.

Looking through the list, skin and appendages, 3.3 percent rate of discontinuation, so again due to rash. So, when you add these together, rash or skin and appendages plus digestive system, and then the adverse venous events, does that help, Dr. Norden?

DR. NORDEN: Yes. Thank you.

DR. RELLER: Dr. Talbot correctly pointed out that the labeling puts some fair declaration of the boundaries of the risk, but it seems to me there is a limit to let the prescriber beware, and some of the boundaries have to do with need, as well as seriousness, and, Dr. Talbot, the data that you presented helps us to weigh that balance.

Dr. Savarese.

DR. SAVARESE: You may have just said what I was

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going to say. The risk-benefit analysis regarding safety for Synercid, yes, a number of patients did discontinue treatment, but they could discontinue treatment, and that is not necessarily a bad thing.

There are adverse reactions which are very bad things that can happen to patients. You wipe out their white cells, you wipe out their liver, you can do nasty, nasty things, so discontinuations are not all the same.

You can discontinue for very, very bad things, so that the safety here I think we should not look at the discontinuations as a sign necessarily of a very bad thing happening, which could have occurred, it is a property of the drug, but it certainly is not a safety issue in what you would consider to be the real classical safety concerns of doing irreparable damage to a patient. That is what goes into the risk-benefit analysis, not so much that the patient gets a rash.

DR. RELLER: Dr. Lumpkin.

DR. LUMPKIN: I think the reason we were asking this is more from the perspective of looking at discontinuations or whatever it happens to be here, is a final issue at the end of the day.

If you have got a drug that is shown to have equivalence on the efficacy side, so it is offering the

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clinician, it is offering the patient nothing more than what the comparator can offer, then, we have to come up with a way of answering the question what is the value of a drug that appears then to have twice the adverse event profile, is there a reason to approve a drug for an indication given that kind of situation and what the clinical alternatives are from a safety perspective.

Again, I am not getting into a comparative efficacy standard. We know that is not one of our regulatory standards, but I do think we have to ask comparative safety standards when we start trying to put this together, and that was one of the major concerns that the review team has had in looking at these more standard indications, again not trying to throw dispersions on the VREF that we will get to later, but on the more standard indications, that question of if efficacy is equivalent, what is the reason, then, for saying that there is a safe and effective product with a safety profile that is twice the comparator.

DR. RELER: Dr. Murray.

DR. MURRAY: I am not a voting member, but I think your problem is even more difficult than you pose in a way because if this drug had not other benefit, if this were the only thing it were being studied for, it might be a simpler

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question to ask, but I think it gets back to the more philosophical question of what does it do to this product, what it does to products in the pipeline if--I am emotionally probably more interested in the enterococcus, so I am willing to sort of give a little on the nonlethal adverse side effects because I realize that if this drug is only for VRE, it won't make it, and the next company won't go after the next drug.

So, I have difficulty myself separating those, but since I don't vote, that is probably okay.

[Laughter.]

DR. RELLER: I have a question for Dr. Chikami. The committee has each of these questions in two parts. I assume that the answers to the parts need not be the same. For those of you who are concerned, I am mindful of the hour and I think if we get some of these issues taken care of on Question No. 1, it will make it simpler for Questions 2, 3, and 4. Don't worry.

DR. CHIKAMI: I guess our intent of structuring the questions this way is, in fact, yes, they may have different answers. I think in general, though, if the committee determines that the data presented to them show that they can conclude from the data that the drug is safe and effective for the requested indication, then, in

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general, that leads to the recommendation that the drug be approved for that indication.

DR. RELLER: Thank you.

Dr. Talbot.

DR. TALBOT: With some trepidation, I would like to support Dr. Murray's comments, and having been involved with the VREF program, I have to tell you that we did rise to the challenge there with FDA. We have enrolled thousands of patients, given the drug to thousands of patients.

If we were not pursuing that indication, and had not studied it, and brought these data to you, would these sorts of questions be asked of us?

DR. RELLER: Any other comments?

The time has come. Part (a). Skin and skin structures. Do the studies support the safety and efficacy of Synercid for skin and skin structure infections? There are 10 voting persons around the table, 8 committee members and 2 voting consultants.

The tradition is to have a show of hands. All of those to indicate your vote with the prerogative of as appropriate to ask for clarification of vote if there is some controversial issues that need to be elucidated. It is sort of in the lines of potentially a minority report if that be the case.

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So, Question 1(a). Those who feel that this safety and efficacy have been adequately presented for Synercid for skin and skin structure, those in favor.

[Show of hands.]

DR. RELLER: Seven.

Those who do not think safety and efficacy have been demonstrated, please raise your hands.

[Show of hands.]

DR. RELLER: Two.

Those who abstain from the vote?

[One abstaining.]

DR. RELLER: And your abstention, Dr. Parker, is because?

DR. PARKER: I am abstaining because I think statistically, they met the criterion, but I don't feel that I should be making a judgment about the safety. I will leave that to the medical people.

DR. RELLER: Thank you.

Now, Part (b), closely related to the above, but not necessarily exactly the same. Does the committee, all things considered, recommend approval of Synercid for the indication of skin and skin structure infections?

Those who recommend that the FDA approve Synercid, please raise your hand.

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[Show of hands.]

DR. RELER: Six.

Those who do not recommend that Synercid be approved for this indication, please raise your hand.

[Show of hands.]

DR. RELER: Four.

Dr. Chikami, that is the committee's position. May we move on to the second question, or do you have something you want to ask?

DR. CHIKAMI: No, I think we can move on to the next question.

Community-acquired pneumonia. The discussion, like Question No. 1, is open.

Dr. Soper generously began what is an ensuing hour's worth of vigorous discussion, just over an hour. We won't ask him to begin discussion of 2.

Dr. Norden.

DR. NORDEN: Like I said, that I thought skin and soft tissue was relatively straightforward, I think this one is also straightforward, but I lean in the opposite direction. I think that the sponsor has not demonstrated equivalence in two studies.

I am concerned about hemophilus, which is certainly a major pathogen and player in community-acquired

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pneumonia and for which Synercid has some activity, but certainly not great activity, and I am concerned about the request for monomicrobic Strep pneumoniae as an indication.

I tried to analyze the data using the FDA numbers, and it looked to me--it is hard to do it--but it looked to me as though the success rate for the two studies for Synercid for Strep pneumoniae was about 80 percent, and for the comparator was about 93 percent, which is not different given the fact that there are only about 56 and 41 patients in the two arms respectively, so it is a small number.

But I also think that we have to look at it in the context and that Synercid is just not clinically a drug that I would think about using for community-acquired pneumonia, certainly not as a primary agent. So, I will start throwing that out.

DR. RELLER: Thank you, Carl.

Other perspectives? Dr. Soper.

DR. SOPER: I have a question about Chlamydia pneumoniae and the way that diagnosis was made. Was it a 4-fold rise in serology?

DR. TALBOT: I can show you the exact serologic criteria for each of the atypical organisms, but yes, 4-fold rise. When IgM assays were available, as I guess for Mycoplasma, we would use a single positive.

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If you care to see all the exact criteria, I would be happy to share them with you.

DR. SOPER: I think you gave us the Legionella, but I didn't realize that Chlamydia was evaluated the same way.

DR. RAKOWSKY: Actually, in response to Dr. Soper, at least in Study 302, when it comes to the serological confirmations, about two-thirds of the patients were diagnosed on elevated IgM for both Chlamydia and Mycoplasma, and about a third due to 4-fold rise in titer. There were agreed upon IgM levels that both us and the sponsor used.

DR. THOMPSON: That is also true of Study 303.

DR. RELLER: Dr. Chesney.

DR. CHESNEY: I was just going to echo Dr. Norden's concern about the pneumococcus with as high as a 47 percent penicillin resistance rate. I think if you had a large number of patients who had had penicillin-resistant organisms, who had responded well to Synercid, that would be very convincing, but without the information, I also would have concerns about approving it for community-acquired pneumonia.

DR. RELLER: Dr. Talbot.

DR. TALBOT: Thank you, Dr. Reller. With regard

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to the last point, of course, we would not request penicillin-resistant strains in labeling. I understand the clinical point.

I would like to clarify that the sponsor is not asking for a broad CAP indication. As I stated in my summary, we agree completely with FDA and with Dr. Norden that this is not a drug that should be used for empiric monotherapy of CAP. We have only one trial showing equivalence.

So, as I asked the committee during my presentation, a question to you and our request to FDA, is really whether it would be useful for clinicians to be aware that when a patient had proven Strep pneumoniae, and needed an alternative drug, that Synercid could possibly be used.

This is obviously a very small selected group of patients, but with the issues about treatment options in Strep pneumoniae now, it seemed to us, and it has seemed to some of our external advisers who have looked at the data with us, that it might be useful to reflect this somehow in labeling, and that is the genesis of our request.

It is certainly not for empiric therapy of CAP.

DR. RAKOWSKY: I think it is important to separate the practice of medicine and the regulatory indications as stated, and I agree that information to clinicians is

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important, but on the other hand, indications with 30-odd, as they stand now, if there was a circumstance where the information would be of vital importance, for example, as Dr. Chesney mentioned, with highly drug-resistant Strep pneumonia, then, we could see the reason to offset the traditional indications, at least put the information in the label.

For a monomicrobial Strep pneumo, the vast majority of which was pen-susceptible, the justice to other companies has to come into the picture here in terms of how do we interpret the 30-odd indications that we have already have in place and have defined in place, and community-acquired pneumonia is one of those indications where we look for a broad overall--efficacy against a broad overall indication except for circumstances where we are looking at a specific resistant organism of major public health concern.

DR. RELLER: Dr. Judson.

DR. JUDSON: If the sponsor is not asking for this indication, why do we have to consider it?

DR. RELLER: We have been posed the question. I think we should deal with it in its entirety. You will recall on the Question 1 there was a structural anatomic clinical cluster, I mean an entity caused by multiple organisms, and we did not divide that by organism, and I

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think we need to address this question in its entirety, and if we think that there are any refinements, we can present that as a recommendation to the FDA.

Dr. Talbot, you presented detailed information on adverse reactions in skin and skin structure infection. One of the questions raised by the medical reviewer was again the differences in adverse effects, serious, not so serious, as it turns out when the data are seen.

Do you have those comparative adverse events for community-acquired pneumonia and possibly even specifically for those infections caused solely by *Streptococcus pneumoniae*?

DR. TALBOT: We have the former, but not the latter. Would you wish to see them, sir?

DR. RELLER: Please.

[Slide.]

DR. TALBOT: This slide is a similar format to the one I showed you a few minutes ago for skin, and it includes results from the pooled studies, 499 patients on Synercid and slightly over 500 in comparator. The number of patients with related adverse events was 21 percent for Synercid and 31.8 percent for comparator, so 4.6 percent for body as a whole, a higher number for comparator.

Remember that the comparator regimen here was

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ceftriaxone and erythromycin, which certainly could be called as standard of practice regimen, and I would also like to remind you that remember in these studies, the investigator had the option to change the comparative regimen, so, for example, if the patient was started on ceftriaxone and erythromycin, and began to have venous intolerability, the investigator could stop the erythromycin and that patient would not be considered as a dropout or as a treatment failure.

Conversely, the ceftriaxone could have been stopped and the erythromycin continued, so the investigator had a lot more flexibility in terms of both efficacy and safety in these studies for the comparator regimen.

Continuing here, digestive system 12.8 versus 25.6, a lot of diarrhea, nausea, and vomiting, again probably reflecting the erythromycin, and that highlights the point that the comparative safety profile is highly dependent upon the comparator regimen chosen.

In this indication, erythromycin is driving a number of these adverse events, but it is the standard of practice regimen.

[Slide.]

On the second slide, skin and appendages, you see here quite similar rates. So, a lot of this difference

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reflected again at the top is driven by the digestive system adverse events.

DR. RELLER: Thank you.

Dr. Savarese.

DR. SAVARESE: Just to reiterate Dr. Judson's comment that RPR is not asking you for this indication, so please take the vote, the but the indication that was posed in the labeling was, as was mentioned before, for culture-proven monomicrobial *Streptococcus pneumoniae*.

The reason that that was done, and was said before by Dr. Talbot, was that we felt that this information could be valuable to the prescribing clinician who is dealing with patients hospitalized with pneumococcal pneumonia, where, in fact, it may be penicillin resistant.

That information may be very valuable and where to put that into the label is not very clear. We had offered that it perhaps be an indication, so that the prescribing physician would see that upfront, so that is why that was done.

Secondly, you recall that the first study 302, equivalence by the statistical criterion was not demonstrated, however, I believe it is clear that there is effectiveness that has been shown for Synercid. It didn't match up to that of the rigorous comparator, but there was

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effectiveness, it wasn't zero.

In the second study 303, the RPR analysis showed equivalence in an adequate and well-controlled study to the comparator regimen, demonstrating effectiveness.

The FDA analysis due to differences in the way that the FDA did that analysis resulted in that study just falling out of the boundary of demonstrating equivalence. In fact, it would take perhaps two or three patient difference from failure to a success that would put it on the other side, so we are dealing with a study that is very close to the demonstration of equivalence.

So, it would seem, in sum, that even for the use in community-acquired pneumonia, some effectiveness has been demonstrated, but we do agree that if we play by the rules, we don't have two equivalent studies, but we feel that effectiveness has been shown and that for the Streptococcus pneumoniae claim, that that is important information that would be of value to the prescribing clinician, and to lose that in labeling we think is of concern.

DR. RELLER: Dr. Parsonnet.

DR. PARSONNET: I have a question in terms of labeling. It seems to me at least when you read a package insert, there are indications for use, and then there is also a section saying which organisms it is active against,

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so that it is possible to put in the list that it is active against Strep pneumonia without actually having it as an indication for monoinfections with Strep pneumonia, is that correct?

DR. CHIKAMI: The way the clinical indications are structured is that studies are done for a specific site of infection, like community-acquired pneumonia. If the criteria are met to demonstrate safety and equivalence in the overall site of infection, then, the data are looked at in terms of the adequacy of the organisms that are usually felt to be etiologic agents at that site, so the indication would read, for example, community-acquired pneumonia due to Streptococcus pneumoniae, Staph aureus, whatever those data support those in the indication section.

I think the other section you are referring to is the clinical microbiology section. Those data, as it is currently structured, there is a first list of microorganisms. That list includes those organisms for which there has been a demonstration of clinical effectiveness, so basically, those organisms which are listed in the clinical indications.

The second list includes those organisms for which there are in vitro data for activity, but, in fact there are no currently adequate and well-controlled clinical trials to

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support clinical effectiveness.

I think that is a long-winded answer to your question.

DR. PARSONNET: That basically means that unless you have it in the first indications, you cannot put it in as having clinical effectiveness in that other section on microbiology, is that correct?

DR. CHIKAMI: Correct. That is the way it is currently structured.

Let me just give you sort of the division's perspective on why this question was structured this way. Clearly, initially, the way that the product was originally developed was to study community-acquired pneumonia, and we reviewed the data that way, as the study set came in.

The question that the sponsor has put forward about monomicrobial infections with Strep pneumo, I think are based on their analyses as they have looked and as they had stated in their slide was a post-hoc analysis.

I think we first want to get the committee's view on whether overall the studies support safety and effectiveness for the indication of community-acquired pneumonia. Subsequently, if the committee wishes to address the second issue, I think that is within their purview.

DR. RELLER: Dr. Chesney, you have your question

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answered?

DR. CHESNEY: I will just say briefly, for those of us that have had a lot of experience with penicillin-resistant pneumococci, we have been looking forward to Synercid for that indication, and I think actually, Julie's question and your response have helped me somewhat in terms of you would be able to put it in there as an in vitro phenomenon, that this drug has activity against penicillin-resistant pneumococci, would that be able to be in the in vitro section? I may not have understood.

DR. CHIKAMI: If, in fact, there were data from in vitro studies that demonstrated activity, and it were an organism--let me give you the short answer--yes, it could go into the second list. It would not go into the first list unless there were data from adequate and well-controlled clinical studies.

DR. RELLER: There is one point that I would like to put forth to keep this discussion in boundaries. When we talk about penicillin-resistant organisms and specifically *Streptococcus pneumoniae*, I think it is worth remembering that the National Committee for Clinical Laboratory Standards' breakpoint definition, they are entirely based on breakpoints consonant with clinical effectiveness of compounds that demonstrate full activity for meningitis

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indication.

As Dr. Gilbert pointed out earlier, he recalled no data whatsoever that the commonly used drugs of choice by consensus recommendations are not effective, all other things being equal in the therapy of community-acquired pneumonia with *Streptococcus pneumoniae*, penicillin susceptible or resistant or intermediate by meningitis breakpoint criteria.

DR. JUDSON: A couple of points on community-acquired pneumonia. One way I have looked at this for Study 302 is if you, first of all, pull out the Strep pneumo cases, you are down to 96 out of 131 were clinically successful.

Doing that and assuming that in that residual group from the data you showed earlier, that *Chlamydia pneumoniae* and *Mycoplasma* now are ranked number one and two, I just wanted to say that equivalency isn't the same as efficacy, and this study wasn't using serologic responses in a position to evaluate efficacy for either the sponsor's drug or the comparator.

All the serologic studies tell you is that the person may or probably was infected with that agent, and given that the natural history for both of those now number one and number two condition is pretty favorable without

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antibiotic treatment. Most Mycoplasma will get better from other studies. Chlamydia pneumonia may, as well. We have only recently come to know that it even is playing a role in community-acquired pneumonia.

So, I don't think we are in a position to say, if the question is phrased efficacy, I don't think we are in a position to say anything about the new drug in terms of efficacy with non-Streptococcal pneumonia, Chlamydia-acquired pneumonia.

DR. RELLER: Other discussion from the committee?

DR. SAVARESE: Just one point. The placement of Strep pneumoniae in the label, as Dr. Chikami mentioned, there would be two places where that could occur, but it would just be a listing of the organism. What would not happen would be that there would be no description of the use of Synercid for the treatment of that infection, no description of that, no dosage recommendations, et cetera.

So, to say that will get in a label in a listing really does not mean too much I think to the practicing clinician who would be looking for some guidance.

DR. RELLER: Other comments?

Question 2(a). Do the results of Studies 302 and 303 demonstrate safety and efficacy of Synercid for the treatment of community-acquired pneumonia?

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Those who believe that they do, yes, please raise your hand.

[No response.]

DR. RELLER: Those who do not think such data support that claim?

[Show of hands.]

DR. RELLER: Ten unanimous no.

2(b). Does the committee recommend approval of Synercid for this indication? Those who vote yes?

[No response.]

DR. RELLER: The nays?

[Show of hands.]

DR. RELLER: Unanimous no on 2(b).

Dr. Chikami, do you wish us to answer any other question related to community-acquired pneumonia or the pathogens encountered therein?

DR. CHIKAMI: The division doesn't have any other questions.

DR. RELLER: Thank you.

Question 3, (a) and (b), dealing with the role of Synercid in hospital-acquired pneumonia. Discussion, please.

DR. SOPER: Can you give us a sense of how often imipenem and tobramycin were used in combination with these

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other agents?

DR. TALBOT: The answer is yes, if you will just give us a second, please.

[Slide.]

This slide shows the results for Study 306, the hospital-acquired or nosocomial pneumonia study, showing the frequency of patients in the Synercid and comparator groups exposed to study medication alone, which would be Synercid plus aztreonam or vanco plus aztreonam--pardon me--this is Synercid alone, vanco alone, 12 and 13 study medication plus anti-gram-negative were the majority.

Now of these, I will need to show you a separate slide, but I can tell you that the majority of patients therefore received concomitant aztreonam. A minority, a substantial minority received imipenem and/or tobramycin, but before I go out on a limb and speculate, let me show you the data.

[Slide.]

This is the slide I thought I was looking at a moment ago. We see here nosocomial pneumonia, number of patients, range in days, median days of exposure. Synercid alone 12, Synercid plus anti-gram-negative agent 131, Synercid plus imipenem and/or tobra without aztreonam 6, vanco 13, vanco anti-gram-negative 130, vanco plus imipenem

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and/or tobramycin with aztreonam 3.

DR. NORDEN: George, a clarification on that slide. Where it says Synercid plus anti-gram-negative agent or vanco plus anti-gram-negative agent, does that mean that those are patients who just got aztreonam or they would have gotten aztreonam plus either imipenem and/or tobra, because I think that is what Dr. Soper's question was.

DR. TALBOT: Yes, I am sorry if that was not clear. That is aztreonam alone.

DR. NORDEN: Thank you.

DR. RELER: Dr. Judson.

DR. JUDSON: I guess this is a point of clarification from the FDA, but you have really compared two types of dual therapy or combined therapy, and we don't have, in my view, adequate information to know whether Synercid could or should be used as monotherapy.

So, what is the indication? Is the indication in nosocomial pneumonia for Synercid plus some gram-negative agent or specifically aztreonam?

DR. CHIKAMI: In those situations where a drug has been used in combination, then, in fact, the indication would be worded that way. For example, there are some antibiotics which are indicated for the treatment of complicated intra-abdominal infection, and those agents may

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not adequately cover anaerobes.

So, in the design of those clinical trials, they are used in combination with an anaerobe, and such statements are made in the labeling indication.

DR. NORDEN: I think that is really correct. I mean, for example, piperacillin and tazobactam says that it should be used with an aminoglycoside or something else to cover pseudomonas, and I think there is no way the sponsor could do a study with mono--I mean with the exception of imipenem, which has been occasionally tried, there is really nothing that has been used in nosocomial pneumonia by itself, so I think we are stuck with you have got to provide gram-negative coverage.

DR. JUDSON: So, what is the question we are answering then?

DR. NORDEN: I would have thought it was Synercid in combination with anti-gram negative coverage for nosocomial pneumonia, but I think your question, which is a much harder one, is how do you then evaluate the role of Synercid in this combination, since many of these are either polymicrobial or -- you haven't had very many monomicrobial gram-positive infections.

DR. JUDSON: When there is no difference, you can't.

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DR. RELLER: Dr. Rakowsky.

DR. RAKOWSKY: I was just going to mention that actually aztreonam's label mentions that it should be used along with a gram-positive coverage, so use the comparator here.

DR. RELLER: Gordon.

DR. ARCHER: Could I ask for a point of clarification about how specimens were obtained, how often was a protected brush used versus tracheal aspiration versus cough sputum, et cetera?

DR. TALBOT: While we are looking for the slide, the study was performed in both U.S. and Europe, and just by way of introduction, I can tell you that the diagnostic methods did differ between the U.S. and Europe, so that in the U.S., the specimens often were obtained by tracheal aspiration or rarely, since the patients were intubated, by expectoration, whereas, in Europe, where invasive procedures using protected methods are much more common, a higher proportion of patients were assessed by an invasive procedure.

[Slide.]

This is a description of the invasive versus non-invasive respiratory culture methods, first of all, by geographic location. We see the total number of pathogens

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for all methods combined is 346, and it was 156 in Europe, 190 in the United States.

The non-invasive cultures, sputum and endotracheal aspirate, 148, and the majority of these came from the United States.

[Slide.]

In terms of invasive respiratory cultures, there were 162 pathogens. You can see that most of those documented by these methods came from Europe, and the methods used are shown, and included protected specimen brush, distal protected specimen, and broncho-alveolar lavage fluid.

DR. ARCHER: Do you have the breakdown on organism by the various methods?

I guess my concern is that there is a high percentage of Staph aureus identified as the cause of these infections, which if that were obtained from an invasive specimen, would be more attributable as a cause of pneumonia. A lot of the studies that I have read show that Staph aureus is no more than 20 percent of a cause of hospital-acquired pneumonia.

So, what I am wondering is, is if a lot of the Staph aureus was from an endotracheal specimen, which is more likely to sample just colonization rather than

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infection. Therefore, some of the efficacy rates could be explained by not eradicating Staph aureus, because it is not really a pathogen, but is a contaminant, or a colonizer, which would be much more difficult to eradicate by any therapy.

DR. TALBOT: I think that is a good point. We have the study report here. We can look for that specifically if we can come back to that question, Mr. Chairman. I think you do raise a good point, Dr. Archer, which is that again, FDA has chosen clinical response in the bacteriologically evaluable population as the primary efficacy parameter.

They may wish to comment, but our inference is that again clinical response is the more reliable parameter, outcome parameter, because sampling of these patients at the time of cure may encounter just the problem you describe, which is endotracheal tube colonization as opposed to actual persistence of the pathogen in the lower respiratory tract.

So, Dr. Reller, may we look for that information and come back if you wish?

DR. RELLER: Please, and while you are obtaining that, Dr. Talbot, could you refresh our memory on the distribution of organisms in the nosocomial pneumonia?

DR. TALBOT: Yes, again, if you will give a

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second, please.

DR. RELLER: I mean if you have it by Europe and the States, if that is separated out, that would be great, because it would be a surrogate for sputum versus bronchoscopic attempt at diagnosis pre-therapy.

[Slide.]

DR. TALBOT: This is not just a delaying tactic. I did want to tell you what our evaluable criteria were bacteriologically to try, as a prelude to the actual answer, to give you some reassurance about our criteria for evaluability.

The baseline causative gram-positive pathogen could be isolated from quantitative lower respiratory tract cultures included expectorated sputum, endotracheal aspirate, or transtracheal aspirate at a count above 10^6 . For protected brush specimen or distal protected specimen, it was greater than 10^3 , and for conventional or protected BAL, it was greater than 10^4 . It could also be isolated from pleural fluid, transthoracic needle aspiration, or open lung biopsy. So, these criteria we felt were really quite rigorous.

[Slide.]

This slide shows the distribution of most frequently identified pathogens at baseline in the two

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treatment groups. There were 87 patients in the bacteriologically evaluable patient population for Synercid, 84 for comparator. The number of pathogens, of course, exceeded the number of patients. Staph aureus accounted for 52 or 38.5 percent of the pathogens in the Synercid group, and 55 and a similar percentage in the comparator group. There were smaller numbers of H. flu, pseudomonas aeruginosa and Streptomoniae.

We will have to look at the geographic distribution of the specimen distribution. I am pretty sure we have that in the study report.

DR. RELLER: Dr. Talbot, I don't expect you have a slide breaking this down, but did the Gram stain smear on those specimens, not the bronchoscopic ones, but the ones from the United States, what role, if any, did that play in interpreting the etiology of these pneumonias?

DR. TALBOT: I will give you my response and then ask my colleagues to correct me if I am wrong, but the Washington criteria, greater than 25, less than 10, were applied to the more classic, potentially contaminated specimens, such as sputum or transtracheal aspiration.

We did not apply those to specimens obtained by the distal protected methods.

DR. RELLER: I am thinking more in terms of one

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isolates organisms, did they mean anything or not, and which one in a mixture is the real culprit. Any comments on how that was addressed in terms of designate a patient as having pneumonia owing to Staph aureus, or whatever? I think one of the questions Dr. Archer raised before, and I would like some discussion after these slides are presented, is this the distribution of organisms that you expect at the outset for nosocomial pneumonia?

DR. ARCHER: I actually had the same question you did, and I guess the simple question is, was the Gram stain used only to evaluate polymorphonuclear versus epithelial cells or was it also used to look for bacteria in the specimen?

DR. TALBOT: The criterion was the colony count growth.

DR. ARCHER: So, you didn't actually look at the specimen for what Gram stain characteristic of organisms was seen?

DR. TALBOT: Fortunately, I have the study leader and my co-project leader here. Yes, there had to be evidence of gram-positive organisms on the stain, and in fact, this was a selected population in the sense that it wasn't just all comers with nosocomial pneumonia who were enrolled. There was a specific effort made to identify

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those who were like to have gram-positive pneumonia, because the focus was to study patients with gram-positive pneumonia.

DR. ARCHER: I think this is an editorial comment. This is what Dr. Judson said about skin and skin structures. I think hospital-acquired pneumonia is the messiest bag of all, and trying to decide what organism is causing infection by whatever study you look at is very difficult, and I don't know that a cutoff of 10^6 endotracheal aspirate necessarily tells you it is a colonizer versus an infector, but I don't know a better way to make that assessment, and I think it is still going to be a very--if you know a way to tell what organism is causing hospital-acquired pneumonia, I think we would all be--I think it is very difficult, but I think this is fairly high for Staph aureus from other studies that I have seen that have looked at protected brush.

DR. TALBOT: You are correct, and it is because of the way the patients were attempted to be enrolled, and just again as an editorial note, as you have mentioned, this was a global study and I could imagine that the discussion we would be having with MCA would be very different, namely, you know, why are those Americans doing all those sputums. There really is a very different approach to diagnosis of this entity in the U.S. and Europe, and that's reflected in

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the types of specimens which are obtained here.

My impression is that a lot of ICU physicians are relative agnostics with regard to the ability to define a bacteriologic etiology of this process, whereas, in Europe, in fact, they rely heavily on the invasive methods and feel that they can delineate an etiologic pathogen.

DR. RELLER: Nonetheless, in these patients, even though there was an attempt to get gram-positive pneumonias because of the spectrum of activity of the drug, the investigators felt compelled 90 percent of the time to add aztreonam to their therapy.

DR. TALBOT: Yes, that is correct, and I think that that is reasonable. These patients have a very high mortality which can approach 50 percent. It was 25 percent in these studies. It would not be clinically or ethically justifiable in most settings to initiate specific therapy as opposed to broader spectrum expectant therapy, so I think as someone mentioned, Dr. Norden perhaps, we would not have been able to do the study if it had been Synercid versus vanco.

We attempted to eliminate some confounding by choosing aztreonam as the agent to be given in combination with the primary study drug, because aztreonam has no anti-gram-positive activity. So, that was an attempt to

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eliminate confusion in interpretation of the results.

DR. RAKOWSKY: To respond back to Dr. Archer's concerns, as well, we looked at the micro criterion differently, where we used greater than 10 epithelial cells criterion as a contaminant for all specimens, and any specimen that grew three or more organisms was thrown out unless there was a predominance of one pathogen, and using different criterion than the sponsor, we also had Staph aureus as by far the most common pathogen.

Our numbers are smaller, 36 in the Synercid arm and 41 in the comparator were fully evaluable for Staph aureus, and then the gram-negatives are comparable to what RPR has. So, using different criterion which again are debatable either way, but similar numbers came out in the long run even though a lower percentage.

DR. ARCHER: Right. That still doesn't necessarily establish it as the etiology. It just means it grows really well in the upper respiratory tract as a colonizer.

DR. RAKOWSKY: Good point.

DR. ARCHER: But I don't any other better way to make the assessment.

DR. PARSONNET: I have a quick question. A proportion of aztreonam is created by the liver, and I was

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wondering if you had any sense of whether Synercid changed the serum levels of aztreonam in the patients that had both.

DR. TALBOT: I am pleased to turn the microphone over to Dr. Rhodes to answer that question. We certainly did not assess aztreonam levels, but Dr. Rhodes can comment on the possibility of a pharmacokinetic interaction. I think I know the answer, but I am going to let him comment.

DR. RELLER: Dr. Talbot, while Dr. Rhodes is coming forward, maybe you could search the database. We will be coming to the adverse effects.

DR. TALBOT: Okay. It takes me two indications, but I learn eventually.

DR. RHODES: I guess the answer to the question is we don't have any direct measurements of plasma increases, but I don't believe that it is a 3A4 substrate, so there wouldn't be a metabolic interaction. Whether there is an interaction in terms of biliary excretion, I don't think I could answer that at the moment.

DR. RAKOWSKY: I can throw out my adverse event slide if you want. It may be a little more concise.

DR. RELLER: We will look at both. We want to address this thoroughly. That is half of the equation having to do with the question.

DR. TALBOT: While we are getting this slide up,

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we can answer Dr. Archer's question, but I am going to have to do it verbally. I apologize. Pathogens were identified by a number of methods. Focusing specifically on Staph aureus, in terms of blood cultures, this is in the all-treated population, 9 pathogens of 173 were identified by blood culture in the Synercid group, 8 of those were Staph aureus.

For the comparator group, it was 22 pathogens of 173, 18 of those were Staph aureus. For protected specimen brush, 39 pathogens were identified in the Synercid group, 16 of those were Staph aureus. In the comparator group, 24 by protected specimen brush, 9 were Staph aureus.

For distal protected specimen, 5 pathogens, 3 of which were Staph aureus for Synercid, 7 pathogens, 2 of them were Staph aureus for comparator.

For broncho-alveolar lavage fluid, 46 pathogens for Synercid, 11 were Staph aureus, 41 pathogens for comparator, 11 were Staph aureus.

For sputum and transtracheal aspirate, 72 pathogens in the Synercid group, 30 were Staph aureus; 76 pathogens in the comparator group, 29 were Staph aureus. So, there was a high frequency of isolation from "good" specimens, and in the sputum and tracheal aspirate group, there was a balance.

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Alex, do you want to go first?

[Slide.]

DR. RAKOWSKY: This is for the non-venous adverse events. The overall related to Synercid was 26 percent, and the comparator, 6.1. We listed the three most common systems involved by just the skin and muscular system, and the number of deaths is listed as is above.

DR. RELLER: Alex, this is assuming that approximately 90 percent of both arms have aztreonam present?

DR. RAKOWSKY: Yes, there are comparable numbers of patients who had aztreonam continue for approximately the median number of days, as well.

DR. RELLER: Which is the majority of them?

DR. RAKOWSKY: Yes.

[Slide.]

This slide deals with venous adverse events, again looking at the patients who actually had a peripheral line, it was 42 percent for Synercid and 28 for the comparator. Discontinuations are as follows: 15 and 9.5. This discontinuation was not related to study drug, discontinuation is listed here.

DR. TALBOT: Thank you, Dr. Rakowsky.

[Slide.]

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The one point I want to mention here is that there was an imbalance in the reporting of related adverse events. Dr. Rakowsky mentioned that, which is 26 versus 6. When we look at all adverse events, non-venous events, and I am not speaking to this slide at the moment.

When you look at all adverse events in these two groups in this study, 96.7 percent of Synercid patients and 93.2 percent of comparator patients experienced one or more adverse events. So, the comparability in the all-event group and the imbalance in the related group does make us wonder whether there was some reporting or, in fact, for the vancomycin arm. We don't know, can't be sure, but we haven't seen that sort of imbalance elsewhere to such an extent.

DR. RELLER: Any further discussion in this regard, efficacy and safety of this compound in combination with aztreonam for hospital-acquired pneumonia?

Question 3(a). Do the data support the claim in safety and efficacy for hospital-acquired pneumonia for Synercid in combination?

Those who believe that the data do support the claim, please raise your hand.

[Show of hands.]

DR. RELLER: Eight.

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Those who do not?

[Show of hands.]

DR. RELLER: Two.

Eight and 2. Fine.

The hospital-acquired pneumonia, does the committee recommend approval of Synercid for this indication? My understanding is hospital-acquired pneumonia in combination with a gram-negative agent.

DR. CHIKAMI: Right. There would be wording in the label.

DR. RELLER: Something along those lines.

DR. CHIKAMI: Correct.

DR. RELLER: Those who recommend approval, please raise your hand.

[Show of hands.]

DR. RELLER: Seven.

Those who recommend against approval, please raise your hand.

[Show of hands.]

DR. RELLER: Three.

The vote is recommend approval 7 yes, 3 no.

Question 4. Vancomycin-resistant Enterococcus faecium infections and the efficacy in a wide range of sites of infection of Synercid in non-comparative studies.

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Carl.

DR. NORDEN: Obviously, we have left the hardest for the end. The reason I think this is so difficult--and I am sure it is obvious--is that there is no comparator. So, we are looking at rates of success in multiple different indications, and we are also left with two different sets of numbers, the FDA numbers, which are substantially lower overall than the company's numbers.

If you look at them, the FDA's numbers--I tried to do this again, putting it all together, which probably isn't valid to pool everything--is about 50 some-odd percent, and the company's is about 70 some-odd percent.

You say 50 percent isn't very good, 70 percent is a lot better, and I don't know where the truth lies. I mean I don't know which is more realistic. I think some of the FDA criteria for evaluability are questionable, things like removal of a prosthetic joint being considered a failure. I think some people would argue it is standard of care. Removal of the catheter.

Those aren't a lot of patients, though, so I am not sure they would change things dramatically, and I think the problem is more of evaluability, and fewer patients evaluable by the FDA.

I think all of us who are taking care of patients

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and C-VREF infections feel, one, they are very hard to evaluate, and two, that we don't have enough good agents, and I think if we were to take minocycline or chloramphenicol, which are our two agents now, that we probably wouldn't do any better, and we might have the same difficulty evaluating them.

So, I guess I would really in a sense like to throw this back--I told Dr. Murray I was going to do this--and try to get her sense from this data, do you think Synercid has really made a difference, and can we really say anything, because I know where I come down emotionally on this, it is clear.

DR. MURRAY: It is much easier to I think have an emotional reaction, and I have the same reaction. I think it is very difficult to tell other than in endocarditis where a drug is working in this organism.

On the other hand, I certainly get a lot of calls on severe infections that aren't responding to other antibiotics, and I think the need is there, and I would want to have the drug available, and I think as was said for penicillin-resistant pneumococci, one has been waiting sort of to have this drug more available, but I think in many patients, it is difficult to tell for the problems that I went through this morning.

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DR. NORDEN: Can I just add one more thing that I think encouraged me, and I think Dr. Rakowsky's analysis was really very helpful, and that is the number of patients with negative blood cultures in the unevaluable group, but prior to either stop it at the time they were discontinued or at death.

I saw your caveat about the resins and not knowing whether this is just residual Synercid in the blood culture bottles and whether it inactivates it, but somehow I don't think that is really the issue.

I came out again with something like 85 percent of the patients having sterile blood cultures, and that is to me impressive. So, I think that is probably to me in some ways the best indication of efficacy that we have.

DR. RELLER: Dr. Murray, did you intend to say that we have been looking a long time for this compound for pneumococci?

DR. MURRAY: No. That statement was made earlier by Dr. Chesney.

DR. RELLER: The reason I raise that is to get everything out on the table. I mean clearly in this question is the issue that is a followup to the meeting having to do with drug development for resistant organisms and where, although the anchors of the regulatory process

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are safety and efficacy, there is also the understanding that there are infections that have developed over the years for which we have a few or no agents.

It is realistically in the equation balancing safety and efficacy, but I wanted to make sure that if we are taking that into consideration, that we clearly delineate where it needs to be taken into consideration owing to paucity or total lack of agents of approved effectiveness.

Resistant *Streptococcus pneumoniae* for a drug that has the pharmacodynamics to treat CNS infections is one thing, but in other sites, another issue. Do you agree?

DR. MURRAY: I just meant that people have been waiting for it to be able to have access to a drug with activity at least in vitro without having to go through a great deal of paperwork that would be required to put a patient on the protocol.

DR. RELLER: For pneumococci?

DR. MURRAY: No, for enterococcus. I was trying to make analogy to a statement that had been said earlier, that people have been waiting for the drug. People are waiting for this drug whether it is emotional or based on data. It is based on I think in vitro and need for a compound.

ajh

DR. RAKOWSKY: For vancomycin-resistant
Enterococcus faecium. Thanks.

DR. CHESNEY: Can I just clarify since I made the
pneumococcal statement? I understand what you are saying.
What I meant to say was that the more we deal with highly
resistant organisms, the more eager we are to have
additional antimicrobials available for our armamentarium.
We already have some for pneumococci for sure. We don't
have any for VREF.

DR. RELLER: I am fully aware and concerned about
resistance, but I think of Franklin Roosevelt's statement,
something about we have nothing to fear but fear itself, and
to raise the specter that every infection, there are no
treatment options, I think concerns me.

DR. PARSONNET: I just have one comment. I think
that the efficacy of this is not as great as everybody would
love to see it, but then oxacillin was only 50 percent
efficacious and something in these studies, so I think
efficacy was pretty toughly stated in these studies.

There is no comparator, but it would be nice to
have a comparator. So, I agree that people are waiting for
this a lot, and I am sure that most people around here have
used this drug and are waiting to try to be able to get it
more easily. I guess that's all I had to say.

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DR. RELLER: One of the issues that comes up for this indication is attributable mortality. Dr. Murray, do you have any further comments on what these resistant enterococci contribute to the morbidity and mortality in patients from whom it has been isolated?

DR. MURRAY: Again, the experience is totally anecdotal, and in my hospital, we don't have a high percentage, so I am not seeing all comers, and I am selected out as someone to call when there is either endocarditis, empyema that continues to grow the organism with pus despite tubes, psoas muscle abscesses that were polymicrobial to begin with that are now solely VRE that are going irrigated and drained, and have been irrigated daily for 10 days. So, I get that call, I get that spectrum.

So, the patients I hear about are selected for those in which the organism has made people ill. I think if you look at studies in the literature, you can find answers on both sides of the table, and one of those studies was shown with the attributed mortality of 37 percent. Another study did not find it with an increased mortality.

So, I have trouble interpreting the literature and my own experience is highly biased for those in whom it is a truth pathogen, and so I think it depends. Yes, some patients it really is an infection, and some patients, I am

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sure some of them, most probably, perhaps most of the monomicrobial bacteremias perhaps do not need to be treated.

I am sure some of the urinary tract isolates would not need to be treated, but other isolates definitely I think do need to be treated. This drug, how much difference it will make, I think I don't know, but I think those patients, there is certainly a population that needs to be treated, would benefit from treatment.

DR. RELLER: Thank you.

Other comments? Dr. Lumpkin.

DR. LUMPKIN: Could I ask a question of the committee? I want to go back to something that Dr. Norden said when he was looking at this, because I think at the end of the day, the emotional aspect here is important and it is something that we are very interested in hearing. I think it is something we probably all share who are in this room today and part of this discussion.

We, at the end of the day, are going to have to have to base a decision on the veracity of the data. I mean if you think a drug needs to be available because you want it, that is one thing. If you think it should be available because the data establish the safety and efficacy of the drug, that is another, and I think that is one area, and to try to get us back on focus to the latter question that I

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put to you, Dr. Norden said earlier that he felt that the strongest evidence of efficacy in the data for this were in the negative blood cultures.

I guess the question I want to ask to you, do you as a committee see clearing of bacteremia as a clinical benefit? I mean is there an efficacy within that element from the spectrum of patients that you see here that that is a clinical benefit, or is that a surrogate for a clinical benefit that is yet to be established?

DR. NORDEN: I think it is a good question. I think it is probably a surrogate. On the other hand, I think it's bad to have bacteremia. It is an obvious truism. I think that Dr. Murray's comment about attributable mortality is correct.

I mean it is very hard to define attributable mortality in any infection, but again, it is probably not--I mean you can't believe that being bacteremic with enterococcus is helping the patient. I think that clearing bacteremia is, for me, not so much that this is a wonderful clinical thing necessarily, but it is a marker that the drug is doing something.

You know, it's like the white count in Pneumococcal pneumonia going down. That isn't what is making the patient better, but it is probably a good

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surrogate. So, I would be comfortable with that, but I think other people may have different or other thoughts.

DR. RELER: Dr. Judson.

DR. JUDSON: I think I might differ in that again the natural history is so variable, and yes, lots of these people do get better without anything.

DR. MURRAY: Although this study I think did restrict themselves to two or more positive blood cultures, is that correct?

DR. TALBOT: That was for the bacteremia of unknown origin category, and the comments about the number of evaluable patients which were made earlier in terms of the traditional indications are relevant here, too.

We met with the advisers whom I mentioned earlier just about two years ago, and the consensus was to try to define a subpopulation of patients in which it was clear that the organism was producing disease, and then try to ascertain response.

So, our bacteriologically evaluable population, as I described to you at the beginning, we really tried to be sure that these patients did not just have the single positive culture. These patients in each indication had clinical signs. They had usually multiple positive cultures, multiple positive cultures over time.

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They had cultures close to the time that Synercid was initiated, and then we followed them and assessed response after that. So, I really feel very comfortable that this bacteriologically evaluable population, especially for some of these indications, represents one in which we can ascertain a response.

DR. SOPER: Do you know how many patients or did you have any patients that relapsed, in other words, they had negative blood cultures, but then they relapsed with bacteremia?

DR. TALBOT: Yes, that did happen, and when we reviewed--in our review process, as I alluded to earlier, we had in front of us all the culture results for every patient, so although we looked at a test of cure window there to match up with the clinical response, we looked beyond that, and if it was clear that, in fact, there was very shortly after the test of cure window a positive culture, we would consider that patient a failure.

We also did look at late recurrences of which there were some. We separated those--and I think this is perhaps another difference with FDA--we separated those out because certainly there are host factors, as well as antimicrobial factors that could affect recurrence, if I have explained myself clearly. It could be continued on,

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drained abscess, or what have you.

So, we did have some. I have the numbers here. It did not materially affect the overall response rates.

If I could make one more comment, just a clarification. Dr. Norden, if you were looking at the numbers in the briefing document for the response rates for us and FDA, there was I think a miscommunication there. Alex, please add in if you want, for Study 301, in particular, the FDA response rates quoted reflected the overall response in the bacteriologically evaluable population.

As I presented today, we feel that that is the most conservative population. What was quoted in the FDA briefing document was clinical response in the clinically evaluable population, and I can show you, if you want to line up the equivalent responses in populations, that in fact, in 301, both our evaluability rates and our response rates are really quite close.

DR. RELLER: Dr. Rakowsky.

DR. RAKOWSKY: I agree with Dr. Talbot on that point, and to respond back to Dr. Soper, I guess the question is do you have a relapse after a patient has been off Synercid in terms of a positive blood culture.

At least for Study 301, for the bacteremias of

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unknown origin, there was no such case where a patient was actually taken off of therapy and then five days or more had a relapse of a positive culture. The failures that I did find in the bacteremia of unknown origin category were all persistencies throughout the entire course of therapy.

I am a little more hazy about the 398-A and B, but for 301, there weren't any of those.

DR. RELER: Dr. Lumpkin, I think I speak on behalf of the committee that we wish to stick to safety and efficacy in evaluating this compound, but we have been denied by the nature of the beast to have the tools with which to do that by conventional criteria.

Do you have some suggestions on how we might objectively go about this?

DR. LUMPKIN: We look at it from conventional in the sense of looking at a comparative analysis. You know, the approaches that we have allow us several different ways of doing well-controlled trials, and historic controls are considered well-controlled trials in the way that we do things.

I think that is one of the ways that would be helpful to us here, but I enjoyed very much listening to Dr. Murray this morning in trying to explain, trying to get a grip on what the natural history of this disease entity is,

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because that is your historic control, and what you are looking at is then it seems in a way the results of these non-comparative trials in essence as compared to the historical control to the natural history of the disease.

I think this is the way we do approach things when it is kind of the first batter up, as it were, against a new indication, a new entity, something that doesn't have a comparator, and it would be interesting, I think, to hear from your perspective how you look at the results, the clinical results and the microbiological results of these trials versus what you know of the natural history of the disease, and then have these patients benefitted.

DR. RELLER: To follow up on that, there are a couple of things that we might put out to the committee for discussion and comment. That is, do you feel from what has been presented, including Dr. Murray's presentation, the literature, as you know it, that the mortality rates and the outcomes with this compound differ substantially from what one would expect historically, or is there overlap?

Another consideration in trying to get at it from another angle is if this drug were to be recommended for approval for VREF, it would become the comparator.

Is that a standard that you would like to see for the future, or is it not a hurdle, that you would like to

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have other things approved by? That is one item.

A third way, and perhaps subjective, but what we are asking, did the investigators think that this drug made any difference in their patients, do you have any data on how many--this was an investigator- or a physician-driven process, as I understand--that is, I have a patient who has an infection for which I do not think there is good treatment. This is a compound that may be effective. I will go through the effort and work to obtain it at no indirect or direct benefit--clarify this if I am interpreting wrongly--and then maybe the next time, after having the experience with that patient, I would have another patient and maybe a second or a third--I know there are not many that have a whole series--and did you get multiple requests, and was there an assessment of whether the investigator felt that if they saw a patient like this again, they would feel compelled to offer that patient the benefit of therapy?

DR. TALBOT: We are not driving the emergency use program. It is driving us at the moment.

[Slide.]

I showed you this slide before. These are spontaneous requests. We are not soliciting requests. I mentioned to you that the number of patients enrolled in the

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fourth quarter of last year was about 100 to 120 a month. The number of requests we get is probably 170 to 180.

I alluded also to the fact that last month we received 188 requests, 130 patients were enrolled, and thus far this month, for a 30-day month, we would be going at a rate of 180 approvals.

The best example I can give you is that Ms. Goldberg here is a member of our emergency use team, and when offered the opportunity to come to Washington or to stay and enroll patients, she decided to join us. It is just a tremendous amount of work, and it is investigator driven.

We have 800 centers. Some of those centers have only had sporadic cases, so we do not hear from them again. Other centers have an endemic problem, and we continue to get requests. I can't say that we get requests for every single patient who has VREF, but we do get repeated requests.

Does that help with your question, Dr. Reller?

DR. RELER: In the endemic centers, you have 5, 10, 15, 20, 30 requests for a given center?

DR. TALBOT: Yes. I am hearing a yes from over here. So, we are adding both new patients at existing centers, and new centers daily.

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DR. RELLER: The experience is growing. Please, comments from the committee about assessment of the effectiveness presented versus the history experience given the lack of comparators.

DR. RAKOWSKY: Dr. Reller, you had mentioned earlier about the historical control for mortality--and, Dr. Murray, please correct me--as far as sizable studies looking at VREF patients, namely, faecium patients, and looking at mortality, I am only aware of two studies that enrolled more than 100 patients.

One was a CDC study by Shay, Montecalvo, Maloney, et al., where the mortality rate is comparable to what was seen in this study, and the other one, unfortunately, was Dr. Moellering & Linden, that presented Synercid data, so we are really down to one non-center study with a n greater than 100 that I am aware of, that you can say this is a large study with at least some statistical power in terms of mortality.

DR. MURRAY: I think Mike Edmond was involved in a study with Dick Wenzel, but the numbers were smaller than 100, you are right, and that was the one with the 37 percent attributable mortality, and one of the problems when you look in the old literature, is what is defined in some of the studies looking at treatment, and most of them have

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looked at bacteremia, is that many of them allowed a single positive culture, details were not known. You didn't know if they had another underlying infection.

What was defined as adequate therapy varied all over the place, some of which I would have thought were adequate and some I might not have thought were adequate.

So, I really can't give you my opinion of what the historical data really show in terms of efficacy of other agents.

DR. RAKOWSKY: And also from our opinion, endpoints are always important, and we have yet to find a sizable study that used what we would consider an appropriate test of cure visit meaning five or more days out.

DR. MURRAY: And all of those would have been--the majority of those would have all been E. faecalis anyway, even if I could give you an answer.

DR. TALBOT: May I comment, Dr. Reller, on this slide?

[Slide.]

There are issues, of course, about what is available in the literature. Probably the most data have been reported with chloro, trying to use a similar approach in terms of assessing clinical and bacteriologic response.

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The Hardalo paper looked at a population of 15 patients, and you can see that only 11 were evaluable. Bacteriologic response was assessed in 6 deaths.

Norris and Lautenbach from the same institution, my alma mater, but I had nothing to do with these studies, of 42 patients, they found only 16 evaluable, and so a clinical response and bacteriologic response of 57 and 73 percent, and similar rates here.

Now, I want to highlight--and you could turn the lights on--is that again these studies are very difficult to interpret even when they attempt to define clinical response and bacteriologic response, because the populations differ.

One thing to remember in looking at our absolute numbers is that we had many, many patients with intra-abdominal infection, and that was the indication with the lowest response rate.

So, if you think of a global number, of a sort of global response rate, it is being skewed by the approximately 40 percent of patients with liver transplantation and intra-abdominal infection.

So, I think I would go back to the point that Dr. Norden made, is having bacteremia good. I think we have clearly demonstrated that the drug is capable of clearing the bloodstream, and certainly the clinicians with whom we

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speaking feel that this is a clinical benefit.

Mortality, for all the reasons mentioned, is a very difficult endpoint to assess. We considered doing that, but except in very selected homogeneous populations, such as one Dr. Linden has studied, that approach would be fraught with methodologic difficulty and the chances of drawing the wrong conclusions. It would be a very, very difficult, if not impossible study, to do.

So, although we do have some exploratory data on mortality, we really feel that the benefit has been shown by all the points I concluded with in my presentation, including the ability to clear the bloodstream.

DR. PARSONNET: Just looking at the types of infections that there were, bacteremia, line infections, endocarditis, abdominal infections, bone, skin, and urinary tract infections, it seems to me that a lot of those, it is very hard to know what the natural history is, and many of those we see, we don't treat, and they get better, and we just don't--especially urinary tract infections, line infections, you pull out the line when you remove the site of infection.

Endocarditis and bone infections, I am usually less likely to think of as spontaneously clearing, and so the fact that they have some efficacy in those is

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interesting to me, but I am really interested in Dr. Murray's sense about this, because of all the people in the room, I am sure you have the most experience with this and have seen the most cases, and have heard about the most cases, so I am just really curious about, in your opinion, when you think about the efficacy against each one of these indications that they have looked at, whether in your experience you think that this does work.

DR. MURRAY: Yes, being anecdotal, of course. I think it probably works for most things except endocarditis.

DR. TALBOT: May I just comment? I really want to emphasize the bacteriologically evaluable population. What you say is true in many instances about spontaneous reversion, but we made assiduous efforts to ensure that the bacteriologically evaluable population included patients with repeatedly positive blood cultures right up to the time of treatment.

I would have to remind you this is not like a usual clinical series where an investigator would look back and see what happened in a large group of patients, such as they did at Penn.

These investigators had to call us to get the drug. Now, I don't know if you would agree with me, but I have heard murmurings to this effect, you have to be pretty

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darned sure that you want to treat this patient before you call us and have to go through the FDA and fill out all the paperwork, submit the CVs, fill out the drug shipments, and so forth.

So, I think we are seeing patients whose physicians are convinced that they have real disease.

Dr. Norden, that makes sense?

DR. NORDEN: Yes.

DR. TALBOT: I am sorry, could I also comment? We have Dr. Linden here who has treated over 100 patients, primarily liver transplants with intra-abdominal infection, but he has, in our investigator group, probably the largest experience, if the committee would like to hear his comments.

DR. RELLER: Dr. Linden, Dr. Christie, Dr. Chesney, and while we are preparing that, I realize that approval or not should not hinge on the efficacy in endocarditis, but could you prepare the number of patients with documented endocarditis, preferably with confirmatory findings of valves involved, of what the success rate was.

I think back to the earlier data that Dr. Murray presented that penicillin/ampicillin alone was in the order of 30 percent.

So, Dr. Linden.

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DR. LINDEN: Thank you. My name is Dr. Peter Linden. I am the University of Pittsburgh Medical Center. I am one of the co-directors of the liver transplant ICU.

My comments, we have in the VRE era since about, at my institution, early 1991, and we do have in a way a historical cohort. We didn't have the first available Synercid until October of '93 where we treated our first bacteremic patient.

So this serendipitously provided a serial cohort, if you will, of patients who we essentially--and, of course, many of these were liver transplants, in fact, 70 percent of them were as opposed to 24 percent in a multicenter. So, this is clearly predominant surgical infection with several modalities of therapy which are overlapping and, of course, as we have said, infinitum make an interpretation very difficult.

I also have some caveats, and this is 399 data. This is data that was excluded in the multicenter analysis because it was purely retrospective, and I think the data needs to be looked at in that light.

[Slide.]

So, we are talking about a comparative period beginning January of '91, running out to October of '93, and that is the control n equals 42, and these patients all had

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bacteremia with two or more separate blood cultures or one blood culture with a concomitant tissue site.

On the other side we have 20 QD-treated patients beginning in October of '93 and running out to about December of '94, when the 301 trial began at my institution. These are the demographics and the clinical features, and as you can see, if you can recall from seven hours ago looking at the multicenter demographics, these are worse.

We have 85 percent and 83 percent transplant recipients and about 90 percent of those are liver recipients. We have a 45 percent incidence of shock defined as amino trail pressure less than 60 or pressor dependence. Ventilator dependence is extremely high. Renal failure defined quite crudely in terms of needing artificial kidney support, and, of course, hepatic failure was also a bit player here.

[Slide.]

These the primary sites of infection, and, of course, we are selecting out an abdominal transplant population, so, of course, these are predominantly intra-abdominal. The second most frequent site was bacteremia of unknown origin.

[Slide.]

Bacteriologic features. Interesting, at my

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institution, the majority of our bacteremias, we are using monomicrobial VRE bacteremias. There was no other bug around. Here, we actually have 25 percent having polymicrobial bacteremia in the QD treated group, and 14 percent, and it falls still within the range that one was familiar with, with vanco-susceptible enterococcal series, the primary sites, of course, primarily being in the abdomen, very often polymicrobial.

[Slide.]

These were the other interventions. Of course, a whole variety of antibiotics that these patients were marinated in, unfortunately, for appropriate or inappropriate reasons.

I should point out that there was a much higher use of vancomycin in the control group, and this could be a confounder because this could act as a selector on therapy and favor continued selection of VRE in the control group.

[Slide.]

Other interventions, of course, because this was a complex infection, the majority of these patients received one type of semi-invasive or invasive procedure. Surgical drainage, of course, was the most common, retransplantation. In fact, Dr. Murray alluded to a case where the patient had a hepatectomy and retransplantation and was cured, and we

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have had these instances, as well. So, it is a very complex mix of therapies, as well.

[Slide.]

These are the clinical and bacteriologic outcomes I am going to refer to. The patients, looking just at bloodstream isolates, and these were not as refined and as evaluable as the collection that the multicenter trial was filtered down to, we did see a lower rate of persistent bacteremia only defined as two or more blood cultures with VRE.

In addition, in 14 and 23 patients, who had followup at the primary site, we did see a borderline benefit towards not finding VRE in followup.

[Slide.]

I looked at two types of mortality, accrued in-hospital mortality, which as you can see are prohibitively high here, higher than I believe in the multicenter trial, 65 percent versus 52 percent. Of course, the key row here is associated mortality.

In this study, I defined it as death within seven days of VRE bacteremia, antemortem evidence of VRE tissue infection prior to death, or a post-mortem exam which demonstrated active infection. Again, that was in this very small series with the caveats that I mentioned. We did

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perceive some benefit. The footprints I think are the bacteriologic effects that we observed.

Thank you.

DR. TALBOT: Since Dr. Linden has broached the issue of mortality, I will just take a moment of the committee's time to make two more points.

We firmly believe for the reasons mentioned that benefit can be ascertained from the clinical response and the bacteriologic response, the clearing of the bloodstream. These are the usual parameters applied to the types of infections we studied.

We didn't study just VREF, we studied skin and skin structure, UTI, the usual parameters, but knowing that mortality might come up, we did think about whether there was any way to look at that other than through the data Dr. Linden presented.

We couldn't figure anything out, but we made the observation that, in fact, there was a substantial delay in initiation of treatment in this cohort, the entire cohort, not Dr. Linden's cohort, and that is probably because in the emergency use setting, the investigator had to call us and then get the drug.

So, we looked at the delay in initiation of Synercid treatment from the time of the first positive blood

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culture. I have a curve of that, which I won't show just now, but basically, there was a median delay of five days between the first positive blood culture and the start of treatment, which I think is longer than would generally be accepted clinically as appropriate, and some patients went quite far out.

So, a question we had was could that have impacted mortality, and those are the data that I would like to share with you.

[Slide.]

What we did is hypothesize that patients who were treated earlier might have a lower mortality than patients treated after a longer delay. So, we examined patients who had a delay in treatment from first positive blood culture to Synercid treatment of less than or equal to three days, and compared it to those who had a delay of four or five days, six days, seven days, and greater than or equal to eight days.

We did this analysis of each population. I am showing you the clinically evaluable population here. What you can see in this Kaplan Meier life table analysis is that for patients who had a delay in treatment of less than or equal to three days, the accumulative mortality at 60 days was about 65, 70 percent, if I am reading it correctly,

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whereas, for those who had a delay of eight or more days, the curves diverge rapidly with a rather large difference by 60 days, which is significant to the p 0.068 level.

Now, this is clearly an exploratory analysis, but we think that it is biologically plausible. It was something that intrigued us and might also provide some information on which you could base your decision.

DR. MURRAY: Barth, I need to go, but I wanted to make one other comment, if I could before I leave.

DR. RELLER: Please.

DR. MURRAY: Going back to Julie's question--let me rephrase that. I am convinced that it works in some individual patients based on what is published and what I have seen and what I have heard about.

My problem is which patients really need it and are some of them going to die anyway, but I think I am clear convinced that in specific patients that have been failing to respond to other therapies and continue to be positive cultures, that they do respond, but the overall thing is complicated by the fact that some will get better and some will die regardless.

DR. RELLER: Dr. Christie.

DR. CHRISTIE: I want to talk about children and infants again. I am concerned, because historically, in our

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institution, about 70 percent of the children who have enterococcal bacteremias are less than a year of age, and half of them are less than three months, and half of that number are actually newborns.

This raises concerns with regards to like Synercid displacing bilirubin from banding sites and causing hyperbilirubinemia in these tiny infants, and there are also other issues that I worry about, as well, too.

I notice in these studies, none of them considered patients that were younger than 18 years of age except for the emergency use protocol of which there were 31 patients enrolled, and I guess I wondered if there was any breakdown in these 31 patients with regards to, say, for instance, the site of VRE infection, the efficacy of Synercid in these patients, any adverse events in these patients, are any studies being planned to look specifically at newborns and children, and specifically, what would we do about labeling, because I would imagine that children with VRE should indeed get Synercid?

DR. TALBOT: Yes, you raise many good points. We are acutely aware of the medical need in the pediatric population, and it is why we wanted to show you what we had. Our colleagues from FDA may wish to comment, but generally, the development approach would be to start in adults first

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and then move to children.

I think that has been--in terms of traditional indications--I think that has been a good approach here because, in fact, we have defined the conjugated bilirubin issue as an issue. We can now mention it in labeling, that is something we would definitely need to consider and have, in fact, thought about in terms of any possible development in the neonate with that being much more important there.

So, we are anticipating pediatric development. We need to take a stepwise approach and ensure that we are addressing safety concerns, as well as efficacy.

In terms of the pediatric population, I will show you just a few slides we have here.

[Slide.]

This is the entire population. It shows you 31 total patients with five under the age of 6 months, equal gender distribution. Duration of treatment means 16 days, range of 2 to 41. Most were dosed at Q8 hours.

[Slide.]

The sites of infections are seen here. I will let you just scan down these. Most of these were bacteremia, causative pathogens primarily *E. faecium*.

[Slide.]

Now focusing on the *E. faecium* population, of

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which there are 24, you can see we still had some very young infants, and I would mention parenthetically that there has been a case of VREF meningitis successfully treated with Synercid. It has been published. The demographics and other distributions are similar here.

[Slide.]

Here are the sites of infections. In this group, we see more intra-abdominal infection than we did overall.

[Slide.]

Here are the success rates for VREF alone. In the all-treated group, success was 54 percent, and failure includes indeterminates, and in the evaluable populations, very small numbers, the rates are as shown.

[Slide.]

The overall response is very similar here, 6 of 7. In terms of adverse events, in these patients, the only adverse events reported was basically one, which was burning at the i.v. site. So, thus far, we have no evidence of any signal in the pediatric population of a different adverse event profile, but the numbers clearly are small.

DR. RELLER: Thank you, Dr. Talbot.

Dr. Chesney? No further comment.

Yes, Carl.

DR. NORDEN: I have one more comment because you

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raised as your second question, would one be willing to use Synercid as a comparator, and my answer would be yes, and I think it would make evaluation of other agents infinitely easier, and it will also I suspect help us to answer some of the questions about history, natural history, who would get better without it, but right now I mean we really are operating somewhat blindly.

DR. PARSONNET: Is it legitimate to say we are not sure about the efficacy, but still say we would like to recommend it for approval?

DR. RELLER: We will ask the question in two parts, and you can vote as your mind and heart dictate. It almost seems like a non sequitur, but I mean these are complex issues, and I think we have to give the recommendation as we call it.

Other comments?

The question. 4(a). Do the data from the studies presented provide evidence that Synercid is safe and effective for the treatment in the sites that have been studied--and then it lists a whole number of them for vancomycin-resistant *Enterococcus faecium*.

Those who feel that the data support demonstration objectively of efficacy in these sites with VREF, please raise your hand.

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[Show of hands.]

DR. RELER: Three yes.

Those who do not feel that efficacy and safety have been demonstrated?

[Show of hands.]

DR. RELER: Seven. We have 7 no, 3 yes.

Part (b). Does the committee recommend approval of Synercid for the treatment of patients with vancomycin-resistant *Enterococcus faecium* infections? Those who feel that we should forward a recommendation for approval for this specific indication, please raise your hands.

[Show of hands.]

DR. RELER: We need to have all the hands up again, those who wish to recommend approval.

[Show of hands.]

DR. RELER: Nine.

Those who do not wish to recommend approval?

[One response.]

DR. RELER: One. So 9 to 1 recommending approval for VREF.

DR. LUMPKIN: Dr. Reller, can we ask what it is being approved based on for the record?

DR. RELER: The question is what is the basis of

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recommendation for approval, and I think there we could answer this crisply and we should just go around the table and we can summarize them.

Dr. Soper.

DR. SOPER: I think traditional measures are the randomized clinical trial, which was not available for this data set, and short of that, it is very difficult to say with certainty that this drug is efficacious in the treatment of VRE, but the data certainly is highly suggestive, and I think the requirements are great and that the risk-benefit clearly is in favor of approving this agent for us, at which we are going to get more information about in a better way, and I think even approving this facilitates that.

DR. RELLER: In the interest of time, please add any comments that Dr. Soper has not already made in terms of the issues.

DR. CHRISTIE: There were variable infections of variable rates of efficacy demonstrated due to various reasons. There was no comparator agent. This is the only agent we have, that would be the best that we have, and I guess there is an emotional reaction, as well, too. Taking care of children, I would like to know that there is something that we have that we could give to them.

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DR. RELLER: Dr. Wittner voted no, but do you want to comment or just let your no be as it is, unqualified?

DR. WITTNER: I think the reason I voted no is I don't think the data demonstrates that there is efficacy, and I think the drug is still available on a compassionate use, and I think more data really needs to be generated.

Right now the data is very, very equivocal.

DR. RELLER: Thank you.

Dr. Chesney.

DR. CHESNEY: I was convinced by or felt convinced by three issues. In reading materials before we came here, I agreed with Dr. Norden that there was clearing of bacteremia. The second thing I was convinced was Dr. Talbot's comment that blood cultures were positive until the drug was begun, and then became negative.

Number three, I was impressed with Dr. Linden's data, although they were limited. Those are my three reasons for voting as I did.

DR. RELLER: Dr. Danner.

DR. DANNER: I have nothing to add.

DR. RELLER: Dr. Parsonnet.

DR. PARSONNET: I have nothing to add.

DR. RELLER: Given the clinical imperative because of suggestions in some populations of efficacy, rather than

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doing more of the same, which would be an option under compassionate use, it seemed to me that this was a mechanism to get a comparator to look at whether something is better in the future, and to potentially not perpetuate a demand that is not going to go away, it is only going to grow, and to try to get the data we really want, but honestly don't have in all areas at the present.

Carl.

DR. NORDEN: I have nothing to add. That is well said.

DR. RELER: Any other comments?

If not, I wish to thank all of the presenters from both Rhone-Poulenc and the FDA, also, for the vigorous and complete discussion. I hope we have answered the questions adequately. It is two minutes of 5:00. We will adjourn on time. Tomorrow morning, the closed session for the members, both consultants and voting members of the committee, begins sharply at 8:30 in this room in the morning.

Thank you.

[Whereupon, the 4:58 p.m., the proceedings were recessed, to resume in closed session on Friday, February 20, 1998, at 8:30 a.m.]

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