DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

COPY

ANTI-INFECTIVE DRUGS ADVISORY COMMITTEE

66TH MEETING

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Rosemary Roberts, M.D.
Gary Chikami, M.D.
Sandra Kweder, M.D.

C O N T E N T S

P R O C E E D I N G S

Call to Order and Introductions

DR. CRAIG: I would like to welcome you all to the 66th Anti-Infective Drugs Advisory Committee meeting. The microphones are a little different today. As I understand, you don't have to go ahead and pull it over, and stick the mike directly in front of your mouth in order to be heard, but you do have to push a button to turn it on, and a red light will come on and it will also light up here. So, that is the new equipment that we have.

What I would like to do is mention that there are some so-called, quote, new members to the advisory committee that I would like to recognize. One of them was actually at our last meeting, Gordon Archer from Medical College of Virginia. One of the new members that is here for the first time is Judith O'Fallon, over here from the Mayo Clinic. Her area of expertise is statistics so she is the one that we really do need to sort of keep us on on the straight and narrow. And, our last new members is Barth Reller, who is from Duke and, welcome, we are glad to have you here, Barth.

I would like to sort of get everybody's name onto our tape record. So, if we could get started with Dr. Gerding, give your name and your affiliation, and we will go around the table.

DR. GERDING: I am Dale Gerding. I am from

Northwestern University in Chicago, and the Chicago VA healthcare system.

DR. MILLER: I am Fred Miller. I am a doctor of dermatology in Geisinger Medical Center in the Pen. State Geisinger health system.

DR. RELLER: Barth Reller, Duke University Medical Center.

DR. ARCHER: Gordon Archer, the Medical College of Virginia, Campus of Virginia Commonwealth University.

DR. MURRAY: Barbara Murray, Division of Infectious Diseases, the University of Texas Medical School in Houston.

DR. NORDEN: Carl Norden, Cooper Hospital, University of New Jersey Medical School, Camden, New Jersey.

DR. PARSONNET: Julie Parsonnet, Division of Infectious Diseases, Stanford University.

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

MS. REEDY: Kathleen Reedy, FDA.

DR. CRAIG: Bill Craig, University of Wisconsin.

DR. O'FALLON: Judith O'Fallon, Mayo Clinic.

DR. RODVOLD: Keith Rodvold, University of Illinois, Chicago, consumer rep.

DR. DONG: Li Ming Dong, statistical reviewer, from FDA.

MR. BOSTWICK: David Bostwick. I am a clinical reviewer from FDA.

DR. ROBERTS: Rosemary Roberts, medical team leader for the topicals.

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

DR. KWEDER: I am Sandra Kweder, FDA.

DR. CRAIG: Thank you. Next, Kathleen Reedy will read the conflict of interest statement.

Conflict of Interest Statement

MS. REEDY: 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 for the meeting and all financial interests reported by the participants, it has been determined that all interest in firms regulated by the Center for Drug Evaluation and Research which have been reported by the participants present no potential for a conflict of interest as presented at this meeting.

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

the record.

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

DR. CRAIG: Thank you. Dr. Chikami will give an introduction. Gary?

Introductory Comments

DR. CHIKAMI: Thank you, Dr. Craig, and good morning. I would like to welcome our guests and consultants this morning, and a special welcome to our new members on the committee, many of whom are actually long-time at least consultants or former members of our committee.

I would also like to extend a welcome to the sponsor of this application, Magainin Pharmaceutics, and to those hardy folks in the audience who braved the sudden snow storm which was quite unexpected.

This morning and today we will be hearing the presentation of an application for pexiganan acetate which is a topical product intended to treat infected diabetic foot ulcers.

There are a number of reasons why we are bringing this application before the committee for discussion. First, it is a compound which is the first in its class. It is a unique compound with a unique mechanism of action. Secondly,

the indication that is being sought and its intended use is somewhat unique as well. The studies that were done, that are being discussed today, were in infected diabetic foot ulcers and, moreover, it is a topical product for that indication. Both of these present somewhat unique sorts of challenges in terms of assessing these data from the point of view that there is not a large regulatory history or history of drug development for this particular use or indication.

In looking over approvals for the past few years and the guidance documents that have been generated by the Division, diabetic foot ulcers have been subsumed under the category of complicated skin and skin structure infections. The most recent version of the draft guidance was published last July, and there are currently two products that are approved for complicated skin and skin structure infections. One is piperacillin tazobactam which is an intravenous formulation. The most recent approval is Trovan, a fluoroquinolone with both an IV and oral formulation. Trovan specifically has wording within its indication for the treatment of infected diabetic foot ulcers.

I think the third issue, as you will see as the data are presented both by the applicant and by the Division, is that there are some challenges in the interpretation of the data.

For all of these reasons, we will be asking the committee's advice in terms of not only interpreting the data but also assessing the overall risk-benefit of the intended use of this product in the population that was studied.

We look forward to the data presentations by both the applicant and the Division, and we also look forward to the committee's discussion. Thanks, Dr. Craig.

DR. CRAIG: Thank you, Gary. I guess I would comment, as far as the two guests that we have here. Fred Miller is a voting consultant. So, he will be voting along with the members of the committee. Dale Gerding's papers are not yet approved. So, he is considered a non-voting guest for this meeting but I am sure at some of the subsequent meetings will actually be a voting consultant.

To start it off, one of our guests is actually going to give us background on the problem. This is Fred Miller who is an FDA consultant.

Background

DR. MILLER: I will put the first slide up and then we can adjust the lighting.

[Slide]

Can people see that as well as they are going to be able to where they are situated? I was asked to give an overview in 15 minutes of the diabetic foot ulcerations and

the problems that we face.

I will just begin by saying that the diabetic patient with a properly treated ulcer can usually heal and avoid the amputation that was formerly considered to be the natural sequel to foot ulceration.

[Slide]

The first question you have to ask yourself is how do ulcers form in the diabetic.

[Slide]

The question is, is it a neuropathic ulcer, the result of lack of sensation and abnormal bony prominence, or is it peripheral vascular disease-driven, is it ischemic?

[Slide]

It is interesting that these ulcers will usually be uniquely either ischemic or neuropathic, and if you have a person who has ischemia and neuropathy the ulcer will usually manifest itself as an ischemic ulcer.

[Slide]

Let's look at the ischemic ulcers. The ischemic ulcers are usually on the distal foot. They tend to be punched out. They might have a very adherent black eschar, and these people will have the other changes of ischemia. They will have pallor on elevation. They will have a cool limb. The pulses will be diminished. These folks go immediately to the vascular surgeons with the hope that

after angiography they will be able to do revascularization or angioplasty.

[Slide]

This is a closeup of the ischemic ulcer to show you this adherent black eschar.

[Slide]

This is another ischemic ulcer. This lady was sensate so she had excruciating pain. She had to cut out her shoe; she could not walk at all. And, after a revascularization procedure the wound will begin to heal very, very well with just moist wound therapy.

[Slide]

This is over the next four weeks. You can see the wound is getting smaller --

[Slide]

-- and smaller --

[Slide]

-- and smaller --

[Slide]

-- until it is healed. So, if you have an ischemic ulcer, if you don't have adequate circulation and revascularization is possible the pain will go in the recovery room after the revascularization, and then basic wound care will lead to healing of the ulcer.

I will mention antibiotics because that is what we

are dealing with today. This lady did not have systemic antibiotics or topical during her healing phase.

[Slide]

Now, the neuropathic ulcer is the one that we are going to be most concerned with. This is the one that I see and that most of us see day in and day out. The ischemic ulcers have to be dealt with by the vascular surgeon.

[Slide]

The neuropathic ulcers tend to be on pressure points. They are in the older population. These ulcers have exuberant callus, and these are usually on an insensate foot. The pulses tend to be bounding. Circulation is not an issue here, and the neuropathic ulcers do not result from microvascular disease. They are the result of loss of sensation and abnormal pressure points on the foot.

[Slide]

Here is a closeup to show you. This was over a pressure point. There was a bony protuberance there on the sole, and you can see the exuberant callus here.

[Slide]

Another one that has been debrided -- and many of these will have an iceberg type change. You look at it and it looks as though it is not very big and then when you debride it, and debridement is a sine qua non of therapy, they are much larger. But what you frequently end up with is

something that doesn't look like much more than a deep brush burn if you have debrided them adequately.

[Slide]

How do these neuropathic ulcers form? As I said, there is lack of sensation and then pressure on abnormal bony prominence. They can occur in shoe wear, shoes that don't fit properly.

This is work done at Carville, and they showed that if you have continuous pressure of one pound per square inch for twelve hours any one of us would get necrosis. You take someone who doesn't have any feeling and he or she will have necrosis. And, as these break down they will be erythematous; they can even be purulent as tissue breaks down, but they are not infected. This is just the result of pressure necrosis.

[Slide]

The other thing that happens is these folks don't have sensation so they walk on objects which will penetrate the foot. They might have something in the shoe or they might walk on something. Frequently they will have eye difficulties and they won't be able to see well what they are walking on.

One of our nurses, a couple of years ago, walked on the Jersey coast. She walked from the shore to her room on the hot sand and on the sidewalk and she actually ended

up losing part of her foot because of the burn on an insensate foot.

[Slide]

Most of the time this is what happens, it is just repetitive motion, repetitive pressure on a single area of the foot. Again, this was work that was done at Carville. What you will see, you will see a red spot and then if you keep pounding away on that same area you will begin to get autolysis; you will get breakdown of the skin, and it can look infected when, in fact, it isn't. It is erythema, tissue breakdown and an ulceration.

[Slide]

For most of us, normal sensation protects us and whispers gently to make the unconscious change to a new position or an altered gait. So, if our foot begins to hurt we begin to walk in a different way. We pronate, we supinate. These folks don't. They walk continually on the same pressure points.

[Slide]

Look at this foot. Look at the shape of it. This is a Charcot foot. It is very difficult not to walk on a pressure point here. It is difficult to have a pair of shoes that fits properly. This person should never go barefoot because if he does he is definitely going to get into trouble. He is going to need specially fitted shoes to avoid

the pressure points as much as possible.

[Slide]

How do we treat these neuropathic ulcers? The first thing is you have to debride and you have to be aggressive in your debridement. These people have great circulation. They have bounding pulses. Their feet are warm. They will bleed copiously, but what you do is you just put pressure on them after you have debrided until they stop.

[Slide]

Here is an example. You can see this one on the heel. Look at the callus around it. This is before debridement --

[Slide]

-- and this is after debridement. You see the difference.

[Slide]

In this case, pressure on the heel is very difficult to relieve, and we will frequently put these folks in contact casts, but before putting them in a contact cast you have to debride this. If you put them in a contact cast with a callus like this it is not going to heal. So, you have to get rid of the callus and then relieve pressure.

[Slide]

This is a hemorrhagic callus which will be removed. It is on the first metatarsal. We are removing it.

[Slide]

What we end up with here is this somewhat malodorous, wet callus. This is not infected. He was not treated with an antibiotic.

[Slide]

After it is debrided, after a week or so with off-loading it is healed.

[Slide]

Another one on the toe -- again, you can see the exuberant callus; no sensation at all. This is a pressure point. This has an odor.

[Slide]

It is debrided, and debrided aggressively.

[Slide]

There is the callous.

[Slide]

And, you can see what we end up with. This man was not treated with systemic antibiotics.

[Slide]

At this point he was treated, actually, with just a toe boot and off-loading with a special shoe, and within four to six weeks this was healed.

[Slide]

There was a lady who came in and had her toe packed but these needed to be debrided.

[Slide]

She was on systemic antibiotics.

[Slide]

So we debrided aggressively because she had bone breakdown in this toe.

[Slide]

After debriding it or after opening it we take a curette. We take a rongeur. We go in and take out all the pieces of broken bone. And, if you culture those you will frequently grow staph. from the bone culture.

[Slide]

This is a cluster of pieces of bony fragments.

[Slide]

Here she is after we debrided her.

[Slide]

We packed this with saline gauze.

[Slide]

Toes are easy to heal because, again, you can off-load them with ease.

[Slide]

She is healing.

[Slide]

And, this is when she was healed. Again, this was with the shoe and just saline packing after we had debrided adequately but, again, the sine qua non is adequate

debridement.

[Slide]

You have to remove pressure and friction. How do we do that?

[Slide]

If it is on the first metatarsal head or the fifth metatarsal head or the heel it is very difficult to off-load. We use contact casting.

[Slide]

Here is a gentleman with a fourth and fifth metatarsal head ulcer, and after five to seven weeks of contact casting they heal. But before you contact cast they have to be clean; they have to be aggressively debrided.

[Slide]

Here is the contact cast. This is a three-layered cast that we use.

[Slide]

This was another gentleman who was in a contact cast. This is the way he presented with an ulcer of about ten months duration. You can see all the exuberant callus.

[Slide]

Here he is after seven weeks of contact casting.

[Slide]

This was before. This had to be aggressively debrided.

[Slide]

Here it is when it is healed.

[Slide]

His feet were not misshapen and we were able to get him into running shoes with molded insoles.

[Slide]

Another one -- this one would appear to be almost ready to heal but what she had was bone protruding through this area with granulation tissue.

[Slide]

So, in the clinic setting what we do, we remove that pressure point with a rongeur.

[Slide]

This is the bone, and that space comes together very quickly with just saline packing over a week or two, and she was healed. No antibiotics in that case.

[Slide]

The question is when is an ulcer infected. First of all, we look for clinical signs of inflammation. You look for abnormal wound drainage and you look for purulent material. However, as wounds break down from pressure they will frequently be quite erythematous and they can have purulent like material as the tissue necroses.

These folks, if they are infected, may have flu-like symptoms. They might get pain in a previously

insensitive foot. They might have hyperglycemia. Elevated fever and elevated white count in diabetics might be absent in up to two-thirds of these people even in the face of infection. So, it is usually a clinical diagnosis based on the signs and symptoms.

[Slide]

Bacteria are not equal to infection because if you culture these wounds you know the numbers that you can get; you know the number of bacteria that can be present in the wound.

[Slide]

Culture taking is difficult. Swabs are not adequate. You can aspirate through intact skin but this is not very sensitive. You can do deep curettings. You can do deep biopsy. But, any time you go through the wound itself you are liable to get false-positive results. If you have bone we can actually do histology on the bone and that can be helpful, and culture of the bone. But cultures are difficult to really determine, you know, the certainty of them.

[Slide]

In these superficial ulcers that we are talking about -- and this is from the Joselin group -- about 54 percent of them had Staph. aureus; Gram-negative staph in 42; strep in 31; Gram-negative bacilli in 23 and anaerobes

in 13. So, most of the time we are dealing with staph.

[Slide]

This is a deep-seated infection. This patient needs to be opened. It has to be incised. It has to be drained. It has to be vigorously debrided, and then this person would have IV antibiotics, and it would be cultured both aerobically and anaerobically from deep in the wound.

[Slide]

Antibiotics, however, can never supplant adequate debridement, and that is the problem that we will sometimes see, that a patient will come in with what is felt to be an infected ulcer and be put on antibiotics, and they don't respond to antibiotics because of two things: number one, they have not been adequately debrided and, number two, they have not been off-loaded, and both of those are absolutely imperative if you are going to treat neuropathic ulcers. You have to debride them and you have to off-load them. They can't have pressure or friction on the area or they won't heal.

As I said, many times after what we have debrided what looks like an infected ulcer it is malodorous. That is because of the moisture in the callus -- it is not infected at all and they don't even get antibiotics.

[Slide]

This was a recent case, just within the last

couple of weeks. It began as a neuropathic ulcer but he had bone exposed here. His fifth metatarsal was exposed and he ended up having a resection. He was admitted. They gave him IV antibiotics and then he had a ray resection.

[Slide]

Another case was in the emergency room within the last month. This is a diabetic who actually shoveled snow with boots on. You know, they are never supposed to wear any shoes other than those prescribed and fitted. He wore boots to shovel snow and came in with this ulcer on his pretibial area with the surrounding erythema which was interpreted as cellulitis.

[Slide]

Here is a closeup. He was treated with an antibiotic orally and he was also treated with a topical antibiotic which is approved for traumatic skin wounds. These are easy to treat, number one, because they are not on pressure areas and, number two, this one didn't require a lot of debridement.

[Slide]

Here is his toe and, again, with just minimal debridement and the topical along with the systemic therapy, he responded.

[Slide]

So, the conclusions here: When we face a diabetic

foot ulcer the first thing that everyone must do is assess the vasculature, and if there is peripheral vascular disease that is significant then they must see a vascular surgeon and, hopefully, you will be able to revascularize them either with reconstruction or angioplasty. And, if they can revascularize them, they will invariably heal.

In the neuropathic ulcers you must debride all devitalized tissue and callosities, and you have to relieve all pressure and friction from the site.

The use of antibiotics in our hands is based on the clinical picture -- you know, does the patient have systemic symptoms? Does the erythema go beyond the wound? Is the wound not responding? It becomes a clinical picture.

One of the areas that can be difficult is the issue of Charcot foot where you begin to get a markedly deformed foot. This can get quite erythematous. It can be very, very hot, and it is frequently misinterpreted as cellulitis with or without an ulcer, and it is just the changes that are taking place with the osteopathy of diabetes.

Thank you.

DR. CRAIG: Questions for Dr. Miller from any of the members? Dr. Murray?

DR. MURRAY: Yes, Dr. Miller, I didn't see a large number of those that might be considered just infected

ulcers that might respond to a topical in here.

DR. MILLER: Yes.

DR. MURRAY: The one with the boot with the big area around that, is that an example of one?

DR. MILLER: It is. A lot of it depends upon the site. You know, if you have an ulcer on the plantar surface, that can be very different than the one I showed you on the leg. The leg was actually very easy. That was very acute. He came in very acutely with what appeared to be cellulitis. They actually cultured him with a swab in the ER --

DR. MURRAY: Right, but you did say he got systemic antibiotics.

DR. MILLER: He was given systemic as well as topical.

DR. MURRAY: Is that an example of one you would have been comfortable with in the context of what we are here today for, treating with a topical? I didn't see a picture of the ones that might be most applicable to today.

DR. MILLER: Yes, I think that is the question, would we be comfortable. I think traditionally we have not treated just with topicals. You know, we have used systemics and then the adjunctive therapy might be topical. We use a lot of just saline packing, and we don't use antibiotics that much in these people. We really don't.

The point that I want to make is that a person

comes in with a malodorous draining ulcer, and after you have debrided the callus and you get rid of the malodor, and what looks like a very, very deep wound tends to be not quite so deep. Then if you off-load and just have moist wound care we can heal virtually all of the neuropathic ulcers within five to seven weeks with contact cast or felt or foam, you know, depending upon the way we off-load.

But the two things that I would say repeatedly is that you must debride them. You have to get rid of all of that. It doesn't matter how much antibiotic you use if you have not debrided them and you have to off-load them.

DR. CRAIG: Dr. Archer?

DR. ARCHER: You mentioned the two types of ulcers, one being vascular and the other being neuropathic.

DR. MILLER: Yes.

DR. ARCHER: Where does microvascular disease fit into all of this in a diabetic?

DR. MILLER: The feeling is that -- and the seminal work was done by Logerfo in Boston and I think it was in an '84 New England Journal, where he looked and said that diabetic ulcers are not microvascular disease. For the most part, their vascular disease is large vessel disease. However, they have more tibial vascular disease than the run-of-the-mill or the general population. But it is large vessel disease, and what we see is tremendous results with

revascularization, and now the vascular surgeons are so good that they do grafts even to the dorsalis pedes area.

So, that was the problem, that folks would have neuropathic ulcers -- getting away from those that are truly ischemic. You know, you look at those and you evaluate them and you have an ischemia situation and if you cannot revascularize those they are going to lose the leg, for the most part. But the ones that we are dealing with on a day-to-day basis are the neuropathic ulcers, and they are the ones that have been falsely identified as small vessel disease, and the reason they didn't heal was they did not off-load them and they did not debride them adequately.

One of the studies that came from Carville was where they took patients with Hansen's disease and they took patients with diabetes. The healing time was exactly the same and, yet, you had two distinctly different etiologies. You know, we hardly ever see patients with Hansen's disease but we have a couple of patients with familiar neuropathy. We have patients with congenital spinal problems who are neuropathic, and if you look at their feet they look exactly like the diabetics. You can't tell the difference if you were just to take the foot, and they are certainly not small vessel disease.

So, with the neuropathy it is lack of sensation, and it is abnormal bony prominences and if you off-load

them, which is sometimes more easily said than done because, you know, you are into contact casting or whatever -- it is interesting with the contact casting, you know, you take a wound; you debride it and you put them in a contact cast and you change that cast in a week and then you reapply it and they might stay in it for two to four weeks. You know, there is absolutely no topical or systemic therapy during that time because, first of all, you don't put them in if there is any hint of infection. The only thing they have against their foot, in our situation, is an Unnaboot first, which is zinc oxide and that just protects the foot before we put the plaster and the glass on.

DR. CRAIG: Thank you, Dr. Miller. We now begin the presentation by Magainin Pharmaceuticals. Kenneth Holroyd will be giving the introduction.

Sponsor Presentation

Introduction and Overview

DR. HOLROYD: Thank you, Dr. Craig. Good morning.

[Slide]

My name is Ken Holroyd and, as a representative of Magainin Pharmaceuticals, the applicant for pexiganan acetate cream one percent, it is my pleasure to have the opportunity given by the Division to address the Anti-Infective Drugs Advisory Committee this morning.

[Slide]

Our agenda this morning will be divided in three parts, as shown here. First, I will give about a five-minute overview and introduction on pexiganan acetate cream. Following that, we will have a presentation from Dr. Benjamin Lipsky, from the University of Washington School of Medicine and the Veterans Administration Puget Sound Healthcare System, on diabetic foot ulcers and the medical need for topical therapy, including pexiganan acetate cream one percent for this condition.

Dr. Lipsky was an investigator in the first of our two pivotal trials for pexiganan acetate cream for infected diabetic foot ulcers. Dr. Lipsky also worked closely with Magainin Pharmaceuticals in developing the protocols for our pivotal studies.

Following his presentation, I will then give more detailed information about the development program, including preclinical background, microbiology and, in the most detail, the information from our clinical studies.

[Slide]

Pexiganan acetate is a new chemical entity with five outstanding characteristics, shown here. First, it is an antimicrobial substance which is a member of a novel class of agents, the magainins. The magainins and pexiganan are both members of a larger class of positively charged or cationic antimicrobial peptides which have been shown over

the last decade to commonly defend the skin and mucosal surfaces of animals, ranging from insects to man, against infection.

Magainins were originally discovered as antimicrobial skin peptides in the African clawed frog. Pexiganan is a 22-amino acid linear peptide which is manufactured by chemical peptide synthesis. It works through a unique mechanism of action which involves pore formation in microbial membranes, and through this membrane active mechanism active of action causes destruction of microorganisms.

[Slide]

What was the rationale for developing pexiganan acetate cream for infected diabetic foot ulcers in particular? This is outlined here. First, pexiganan acetate has a broad spectrum of activity against microorganisms, which includes Gram-positive and Gram-negative, aerobic and anaerobic bacteria, as well as certain species of fungi. This seemed perhaps an appropriate match for the polymicrobial infections which can arise in infected diabetic foot ulcers.

Secondly, patients with infected diabetic foot ulcers have the multisystemic complications of diabetes and are not, unfortunately, infrequently in and out of the hospital or receiving courses of other antimicrobial agents.

They are, thus, potentially at higher risk than the average individual for being colonized or infected with bacteria resistant to other antimicrobial classes of agents.

We had a series, which I will show you later, of in vitro data showing activity for pexiganan acetate, being a member of a unique class of agents, against bacteria regardless of their susceptibility or resistance to other agents.

Topical therapy was suggested to us by origin of the magainins from the skin originally discovered in the frog, and we felt that having a topical therapy alternative for patients with infected diabetic foot ulcers may offer a number of potential clinical or microbiological advantages for these patients.

[Slide]

How is pexiganan acetate cream manufactured? This is outlined here. The pexiganan acetate powder drug substance is placed in an aqueous solution to which is added an emulsifying base. After homogenization we have the pexiganan acetate cream one percent.

[Slide]

The components of the cream are shown here, and include the active ingredient pexiganan acetate at a concentration of one percent or 10,000 mcg/mL, and the excipients which include sodium acetate buffer to a pH of 5

and other excipients which provide emulsification, emollient and antioxidant actions. All of the excipients are on the FDA's inactive substances list and are common ingredients in creams.

[Slide]

Pexiganan acetate cream is to be packaged in two sizes, with the 1 percent cream in 7.5 g and 15 g tubes.

[Slide]

During the development program for pexiganan acetate cream Magainin Pharmaceuticals consulted closely with the Division of Anti-Infective Drug Products. Some of the key dates in the regulatory history for the development program are shown here.

In August of 1992, an IND for pexiganan acetate cream for the treatment of superficial and complicated dermatological infections was submitted.

In June of 1993, we initiated the study for the treatment of impetigo. This study resulted in a finding that all study groups, which included 0.51 percent, 2 percent pexiganan acetate cream and a placebo group, had response rates of over 80 percent. We concluded that in this study, done in children in Puerto Rico, impetigo was a self-limiting condition while treated with good hygienic measures.

We then had submitted, previous to the conclusion

of the impetigo study, an IND for the treatment of infected diabetic foot ulcers. We initiated the first pivotal study in August of 1994, and the second pivotal study in August of 1995. These two studies of infected diabetic foot ulcers remain, to our knowledge, the largest studies of antimicrobial therapy for this condition ever conducted.

We worked with the FDA through the pre-new drug application submission process, and the NDA was submitted in July of 1998.

[Slide]

During the course of this morning's presentation I will show you data from our studies which report our indications for pexiganan acetate cream for the topical treatment of patients with infected diabetic foot ulcers.

[Slide]

I would like now, as this concludes our overview and introduction, to introduce Dr. Benjamin Lipsky, from the University of Washington School of Medicine. Dr. Lipsky?

Diabetic Foot Ulcers and Medical Need

DR. LIPSKY: It is a pleasure to be here this morning, speaking to the Division of Anti-Infective Advisory Committee about a topic that may seem pedestrian, if you will, to some but it is one that has been of great interest to me over the last several years.

[Slide]

I have entitled this talk "Evolution in the Management of Diabetic Foot Infections" because in the last two decades what we have seen is the introduction of science to a field that previously was dominated by anecdotal and empirical information, and we have seen a great evolution in our ability to treat these difficult infections.

[Slide]

As you have heard, I am at the University of Washington, seen here on one of the rare sunny days there. We have a group of investigators who, over the last 15 years, have been very interested in diabetic foot infections and we have looked at various aspects of these infections, and I would like to give you some of the information that we have learned in the next 20 minutes.

[Slide]

Perhaps the fist case report of an infected diabetic foot is in the Bible. In Chronicles, it says "in the 39th year of his reign, King Asa became infected with gangrene of his feet. He did not seek the guidance of the Lord, but resorted to physicians. He rested with his forefathers in the 41st year of his reign." My hope is that with the knowledge we have recently gained we can do better than our ancestral physicians.

[Slide]

In the twenty minutes allotted to me, I would like

to discuss the epidemiology, pathophysiology, clinical presentation, microbiology, treatment, and the potential for topical therapy for diabetic foot infections -- a task that is made remarkably easier by the excellent introduction you have already received from Dr. Miller.

[Slide]

Diabetic foot infections are a common and serious problem. It is estimated that there are approximately 16 million diabetic patients in the United States, upwards of a quarter of whom will eventually develop a foot ulceration. The majority of these patients, when they present to their healthcare provider, will have an infection in the ulcer.

The percentage of patients who have deeper infection varies widely but in most studies it is about 20 percent. The cost of treating these infections is substantial. Data from two recent studies suggests that the cost of a particular ulcer episode ranges at about $4,600. In addition, complications of the foot are the number one cause for diabetes-related hospitalizations in the United States. About half of all diabetes hospital days are caused by foot complications. Tragically, amputations, perhaps the worst of the complications of infected diabetic feet, continue to occur at a high rate. It is now estimated that diabetes is responsible for more than half of the approximately 60,000 non-traumatic amputations that still

occur in the United States every year.

[Slide]

Let's dwell a moment on the financial aspects of diabetic foot infections. This is data from a Swedish study, completed in 1995, which tracked patients who had diabetic foot ulcers. In Sweden, many of these patients are hospitalized, and in the first year after they develop their infection you can see that the total cost of care for both inpatient and outpatient care, as well as home care follow-up, was $37,000. But the cost didn't end there. During three years of follow-up costs continued to accrue for these patients regardless of the outcome of the original ulcer.

[Slide]

Perhaps more important than the financial cost, however, is the human cost. This same group of patients was divided into those who had a primarily healed ulcer and those who required an amputation. If we look at the recurrence rate of ulcers over the next 5 years, you can see that those who healed primarily had a recurrent ulcer more than 60 percent of the time. Those who required an amputation had a recurrent ulcer almost 80 percent of the time.

Looking at the amputation rate over the next 5 years, patients who primarily healed with the first ulcer had an amputation more than 10 percent of the time over the

next 5 years, and a remarkable 50 percent of the patients who had had one amputation, unfortunately, required another over the next 5 years.

[Slide]

Why do diabetic patients have problems with their feet? Well, as Dr. Miller outlined very nicely, it is a multi-faceted and complex problem. Angiopathy certainly plays a role and, as Dr. Miller mentioned, microvascular disease is probably not the most important component. Rather, so-called microvascular disease or atherosclerosis of the large vessels, particularly below the knee, is more important in causing the vascular problems that diabetic patients frequently have.

But more important than the vasculopathy is neuropathy. This is in the form of sensory neuropathy causing patients to not feel the rock in their shoe or the too hot bath water; motor neuropathy which causes changes in the shape of the foot so that they can't fit into a normal shoe; and autonomic neuropathy which causes problems with dry skin, poor sweating and arterial venous shunting.

The final common pathway that may lead to amputation is often infection. Breaks in the skin caused by these other problems lead to organisms producing infection. There is a variety of other poorly understood problems that have been called dysmetabolism. Wound healing in diabetic

patients tends to be not as good as in non-diabetic patients. Mechanical stresses are certainly important, as Dr. Miller has pointed out, and unfortunately, in many populations neglect of the feet leads to amputations as well.

[Slide]

This is an x-ray of the kind of patient similar to the one that Dr. Miller showed you. You can see the marked deformity of the foot. High pressure would be exerted in these areas. When this patient presented, he had worn a new pair of shoes for the last several days and when he took them off he noticed the ulcerations across the dorsal surface of his toes which, over the next day or two, produced cellulitis and purulent material. This kind of diabetic foot infection is all too common and this is what the patient presented to our clinic for.

[Slide]

When we examined his other foot, however, he also had this ulceration on his heel of which he was completely unaware. This is the typical ulceration that Dr. Miller spoke about where the body attempts to build a callus to protect that area. Ultimately that fails. A breakdown of the callus leads to a hole in the foot and this is potentially susceptible to the development of infection. Debridement of this kind of lesion is absolutely critical, as you heard.

[Slide]

Let me show you a couple of examples to address Dr. Murray's question about the types of patients who would have been enrolled in a study of a topical antimicrobial agent. Here is a patient who has what appears to be a punched out ulcer that occurs in an area of high pressure on the metatarsal head. You can see a surrounding rim of erythema with a purulent base. This is one type of patient infection that we consider appropriate for topical therapy.

[Slide]

Here is a patient whose toes were pressed together by an improperly fitting pair of shoes who developed an ulceration. Again, there is a rim of erythema with purulent material -- again, another type of patient who might be appropriate for topical therapy.

[Slide]

Well, as I mentioned, infections develop in skin breaks. The organisms that colonize normal skin, including Gram-positive cocci in particular but also some Gram-negative rods then multiply in the area of the skin break to produce the infection which, if unchecked with appropriate local care as well as antimicrobial therapy, can lead to deeper infection with contiguous involvement of the deep soft tissues and ultimately the bone.

[Slide]

We do not define infection microbiologically, as Dr. Miller mentioned, because of the fact that all wounds are colonized by microorganisms. Even virulent organisms such as Staph. aureus may be nonpathogenic in these wounds. Therefore, we resort to a clinical definition. We feel that the presence of purulent secretions or pus which suggests that the body is sending in white cells to fight off the bacteria or the presence of two or more signs of inflammation constitute a reasonable clinical definition of infection.

[Slide]

Infections can be classified in many ways. This one is a simple clinically useful one in which the infections are divided by how serious they appear to be from a clinical point of view. Mild infections involve the superficial layers of the skin, the dermis and the epidermis. When you begin to see involvement of the deeper soft tissues or bone, or potentially some degree of tissue necrosis or gangrene, we think that the infections should be called moderate. Severe infections involve systemic toxicity or evidence of metabolic instability.

[Slide]

If you look at the published studies of foot infections, these are the kinds of patients that most commonly appear. They have a mean age of about 60. They have

had their diabetes for approximately 15-20 years. Most of the patients have a foot ulcer as the original cause of their infection. Interestingly, the infection had been present for more than a month in a third of cases. The majority of patients have some evidence of vascular disease but almost all have evidence of peripheral neuropathy. Almost half of the patients had had previous recent antibiotic therapy which can certainly alter the microbiology of these infections. And, approximately a quarter to a third of the patients will have osteomyelitis, here in quotation marks because of the various ways that that is defined by authors.

[Slide]

Let's talk a little about the microbiology of diabetic foot infections. In order to talk about that we first need to talk about how can you obtain appropriate cultures to know that your microbiological results are clinically useful.

All too often, foot lesions are cultured as shown on this slide. A cotton swab is rolled over the surface of a wound that has not been adequately debrided. What is important is that superficial eschar, foreign material and other material needs to be debrided off the wound, as Dr. Miller has stressed. At that point you can clean off the wound with saline and gauze and then perform a procedure

that is called a curettage, which simply means scraping the base of the wound, here shown with a dermal curette but most easily done with a scalpel blade. That tissue can then be sent to the microbiology lab.

At least three studies have now shown that provides highly accurate microbiological information, similar to that from biopsy tissue. An alternative method, as mentioned by Dr. Miller, is to aspirate any purulent secretion which is a highly specific if not necessarily sensitive method.

[Slide]

If you look in the literature at the results of studies that use appropriate culture and techniques, this is what you will find. Very few infections are caused by anaerobic only. Here is the range and here is the mean in the reported cases in the literature over the past decade.

Some cases are caused by aerobic bacteria alone, but the majority of cases are caused by a combination of aerobic and anaerobic bacteria. You can see that the number of isolates per case ranges from just under 2 to nearly 6, with a mean of about 3, 3.5 per case.

[Slide]

What specific organisms are isolated? Most commonly aerobic Gram-positive cocci, the most important single pathogens. You can see that staphylococci, both

coagulase-positive and coagulase-negative, constitute the most common isolates. Enterococci and staphylococci are frequent as well. But almost two-thirds of the patients will also have aerobic Gram-negative rods, and upwards of about a third can also have anaerobic organisms of various types.

[Slide]

Perhaps a simple way to think about the microbiology of these infections is as follows: Patients who present with mild early infections who have not previously had antibiotic therapy will typically have infections caused by Gram-positive cocci, often alone. But as the infection becomes chronic, and we mentioned that in at least a third of cases that is the situation by the time the physician sees them, or as necrosis develops we begin to see anaerobic organisms and Gram-negative rods become more common.

[Slide]

Now, the bacteria are important but as the father of microbiology, Louis Pasteur, said more than a hundred years ago, "the germ is nothing -- it is the terrain that is everything."

[Slide]

I think that perhaps is an overestimation of the importance of the underlying host resistance, but I think this equation probably neatly summarizes the principles involved. The likelihood of infection is related both to the

total number of microorganisms to their virulence and inversely related to the host resistance, which we know to be reduced in diabetic patients, especially those with long-standing diabetes.

[Slide]

What I would like to do now is speak about the treatment of diabetic foot infections. When I first became interested in this field, having seen a number of patients on the wards with diabetic foot infections, I went to the literature to read about what the appropriate way to treat them was. What the book said at that time was that virtually all patients needed to be hospitalized, and in those pre-DRG days they were hospitalized for upwards of three to six weeks.

It was suggested that virtually all patients needed broad-spectrum therapy, usually administered by the intravenous route, and if the infection failed to respond to therapy amputation was usually necessary. Fortunately, we have made remarkable progress in this field since that time.

When we look at patients with diabetic foot infections, there are three main areas to think about. The first is supportive therapy. The patient with a serious infection who is usually hospitalized typically needs fluid and electrolyte replacement, control of his hypoglycemia and any other metabolic disorders.

The second thing that we should probably think about is does this patient need a surgeon involved in his care. Virtually all patients need some form of debridement. Often incision and drainage is necessary. If bone is exposed, it often needs to be resected by whatever route is most expedient and, as Dr. Miller has mentioned, revascularization can remarkably improve the outcome in these patients.

Then, and only then, do we think about antibiotic therapy which is typically divided into initial therapy which is empirical and later therapy when culture results are back, which can be more definitive.

[Slide]

We know that there are problems with antibiotic therapy. Unfortunately, this doesn't show very well but on the cover of "Newsweek" you may recall this cover showing the question being raised, "Is this the end of miracle drugs?" In other words, does the resistance that is developing in microorganisms spell the outcome of doom for antibiotics?

Well, this cover is from 1994, and certain stories just don't die. This is a persistent issue. If you can read it, up above it says, "Watergate anguish in the White House." Like that story, this one continues on.

[Slide]

What would be an ideal antimicrobial agent? Certainly one that is highly active and rapidly bactericidal. We would like it to cover the appropriate spectrum of organisms causing the types of infections we are using it for. We would like to see effective concentrations at the infected sites. We would like the adverse effects to be minimal or potentially preventable. We would hope that emergence of resistance to the antimicrobial would be unusual, and we would like the cost to be relatively low both for the drug itself and for the route of administration.

[Slide]

Potential oral antibiotics for treatment of mild to moderate diabetic foot infections include those shown on the screen and to some degree, depending upon what you think the likely microbiology is, you can select either relatively narrow agents like one of the semi-synthetic penicillins or cephalosporins, or a somewhat broader spectrum agent such as a fluoroquinolone, or a combination of agents, as shown here.

[Slide]

When you look at what physicians actually are doing, this is the best available data. The prescription drug data base, the most recently available set from the end of 1998, shows the following: For the ICD9 classification of

diabetic foot ulcers, unfortunately not broken down into those that are infected and those thought to be non-infected, 63 percent of all office visits result in an antibiotic being prescribed.

And, what antibiotics are doctors prescribing? Well, in about 20 percent of the cases they are prescribing fluoroquinolones; cephalosporins, 20 percent; penicillins approximately 20 percent. What was of interest to me was that in about 20 percent of cases they are also prescribing topical agents, sometimes alone and sometimes in combination, and you can see the various agents among those that are currently available that are used by physicians in practice.

[Slide]

Why do doctors think about using topical therapy? Well, I think there are a number of reasons for that. There are problems with oral antibiotic therapy, particularly in diabetic patients with foot infections. Gastrointestinal absorption may be inadequate in some patients. Particularly, this may be a problem in the presence of gastroparesis.

We know that tissue penetration of many antibiotics, perhaps with the exception of the fluoroquinolones, may also be inadequate. Several studies show that tissue levels of antibiotics are no more than 20 percent of those found in the serum in diabetic foot

infections.

And, as already mentioned, there is a relatively high prevalence of resistance to the currently available oral antibiotic agents.

[Slide]

This has led us to think about the possibility of topical therapy for appropriately selected patients. The polymicrobial etiology that I have already outlined for these infections suggests that a broad-spectrum antibiotic may well be useful.

We can think about topical antiseptics but the problem with most of those is that they tend to be toxic to the host tissues, killing the epithelial cells that are attempting to close the wound and, therefore, they are not recommended by most experts.

Previous experience with topical antibiotic therapy has been only anecdotal and, therefore, it was important to do a controlled, proper prospective study to see if this would work.

[Slide]

The potential advantages of topical antibiotic therapy for diabetic foot ulcers include the fact that they provide a high local antibiotic concentration. Topical therapy can overcome the potential problems with both absorption and delivery. You can use agents that are not

currently available systemically. You can potentially avoid the systemic adverse effects that are common with some oral antibiotic agents. We also think you can avoid promoting antibiotic resistance to the types of antibiotics that are necessary for treating systemic infections and may not be necessary for treating local infections. Finally, and perhaps in my view most importantly, topical therapy emphasizes the importance of wound care.

[Slide]

I have tried to show on this slide what I mean by that. Typically, when the doctor prescribes an oral antibiotic to the patient the most important member of this triumvirate is left out of the picture. On the other hand, when we have looked at giving topical therapy we involve the patient as well as the physician in dealing with proper wound care and paying attention to the foot.

[Slide]

Well, that leads us to the question of the hour, "can frogs cure people?" In other words, what is the role of a frog-derived synthetic ant pexiganan acetate? Well, I will not steal Ken Holroyd's thunder as he presents to you the results of these carefully conducted trials, but what I would like to do is set a bit of a background and perhaps set the bar.

There is at present only one antibiotic agent that

is specifically approved for the treatment of diabetic foot infections, as previously mentioned, and that is trovafloxicin.

[Slide]

I would like to show you the results of one of the studies submitted in support of that application. I chose this one because it is a similar comparative trial in outpatients of infected foot ulcers without osteomyelitis, presumably some comparable patients to those that we enrolled in our trial.

You can see that at the end of therapy for both trovafloxicin and the comparator agent, Augmentin, approximately 85-90 percent of patients at day 11-15 had a clinical response to therapy. At the end of the study, which was 30 days after enrollment, you can see that about 75-80 percent of the patients had a clinical response to therapy.

These results are quite similar to those that we found in a study published in 1990 comparing oral therapy with cephalexin and clindamycin, again, about 80-85 percent at the end of therapy. I think what you will see is that the trials of pexiganan show a very similar outcome to these trials.

[Slide]

What then is the role of pexiganan in treating infected diabetic foot ulcers? Well, I think I can say as

someone involved in the clinical trials and using this drug, as well as somebody who has reviewed the data fairly carefully, that I think that topical pexiganan appears to be safe and effective in treating appropriately selected infected diabetic foot ulcers. This therapy provides several potential clinical and microbiological advantages over systemic antibiotic therapy.

[Slide]

As you, the committee, think about the process of approving this new agent, I would remind you of the "Doctor's Dilemma," a play by George Bernard Shaw, in which he said, "I marvel that society would pay a surgeon a large sum of money to remove a patient's leg, but nothing to save it." I think we now have a variety of treatments that can help save patients' legs and avoid that tragic outcome.

Thank you very much.

Preclinical Background, Microbiology, Clinical Studies

[Slide]

DR. HOLROYD: Let's move on now to our presentation of the pexiganan acetate cream development program where we will cover the preclinical background, information about microbiology and, finally, the clinical trial information.

[Slide]

Regarding the preclinical background, we will look

at information showing that pexiganan is an analog of the magainin family of peptides, and that both are members of a larger family of cationic antimicrobial peptides. We will then look at information about the mechanism of action of pexiganan and the magainins.

The story of the development of pexiganan begins in 1987, in the laboratory or Dr. Michael Zasloff then head of the Pediatric Genetics Branch at the National Institutes of Health. Dr. Zasloff used the African clawed frog, an animal commonly used for genetic research, to harvest the oocytes for gene expression experiments.

[Slide]

Upon suturing the frog, as shown here, and placing these animals back into an aquarium of microbially contaminated water, he noticed repeatedly that the incisions, as shown below, in this frog one week and one month after the incision was sutured would heal without evidence of infection or inflammation. Dr. Zasloff asked the question could there be antimicrobial substances expressed in the frog skin that could, at least in part, explain this phenomenon.

[Slide]

A series of isolation experiments led to the discovery of the linear peptides which he called magainins. The word magain in Hebrew means shield. Dr. Zasloff felt

that these antimicrobial peptides were providing a shield against infection in the frogs.

Pexiganan acetate is a relative of the originally discovered magainins and the amino acid sequences are shown here for comparison. As you see, all three are linear peptides, the originally discovered magainins 23 amino acids in length; pexiganan 22 amino acids in length. All share the feature of having multiply positively charged lysine residues as shown in yellow. The differences in amino acid sequence between these three peptides are highlighted by the blue arrows. Pexiganan was brought forward into development after an extensive structure activity program involving the synthesis of several thousand peptides conducted at Magainin Pharmaceuticals.

[Slide]

Let's look at how these peptides are used in the frog to defend the skin against infection and prevent infection when the skin is wounded. It has been found that magainins are stored in the so-called granular gland of the frog which sits just underneath the skin surface. These granular glands are discharged in response to skin injury or infection and are controlled by local adrenergic nerve endings.

[Slide]

Let's see how this looks on a closeup view when

they are discharged under the skin surface of the frog. We see here in three panels, first in (a) a closeup of the frog skin with granular glands underneath the surface. Upon wounding of the skin, adrenergic release in response to infection, there is within seconds a discharge of the glands and the granules containing high concentrations of magainins. These then spread out into a film on the surface of the frog, which is not washed off in the aqueous environment, and provides a shield containing a high concentration of antimicrobial peptides.

[Slide]

Let's see how this looks visually for an intact frog, as we see here with the frog in this pharmacologic stimulation, where we place a little bit of adrenaline powder on the back of the frog and it discharges within a matter of a minute this film, this gel containing high concentrations of antimicrobial peptides.

[Slide]

It has been now discovered over the last ten years that all animals that have been examined contain antimicrobial peptides which help in part defend the animals against skim or mucosal infections and colonization. As a class, these are all positively charged peptides which can vary from 12-15 amino acids in length. There is broad use across species, ranging from insects, amphibians,

crustaceans, birds and mammals up through man.

These peptides may either be linear, as in the case of the magainins or as in the case of the human linear antimicrobial peptide known as LL37, or they may be more structured with multiple disulfide bonds, which is the case with the human. They share the characteristic of working through membrane active mechanisms of action which can vary slightly between the different antimicrobial peptides but, because of differences in the external lipid composition of mammalian bacterial cells, have selectivity for microorganisms. They have broad spectrums of activity and may either be constitutively expressed or induced upon injury or infection of the mucosal surface.

[Slide]

Many tissues in higher animals express these antimicrobial peptides, as outlined here. We see here, highlighted in white for three tissues, the expression of antimicrobial peptides. These tissues are all obtained from the cow but the same tissues in man express slightly different antimicrobial peptides.

We see that on the surface of the cornea, and the epithelial lining of the intestine, and here induced around a dermal abscess in the skin of the cow strong expression of antimicrobial peptides. In man these peptides are expressed also in the lining of our lungs, in our oral mucosa and in

our tongue, which provides at least in part an answer to the question as to how we can bite our tongue in a mouth full of bacteria and, yet, rarely sustain an infection.

[Slide]

In general, these antimicrobial barrier defense systems provide a localized defense with a rapid response time against a broad spectrum of organisms, and have been found present in all animals examined for them. This contrasts to the systemic immune system which in general provides a more diffuse response which can take up to several days to develop fully; is specific for specific antigens; and is present predominantly in higher animals but not, for example, in insects.

[Slide]

Over the course of evolution, these cationic antimicrobial peptides have learned to cooperate together with other components of the host defense system, as outlined here where we see in a well diffusion assay where three different antimicrobial peptides have been added, and we see clear zones of synergy between them.

In addition to cooperating with each other, in both man and in animals, antimicrobial peptides have been shown to cooperate with other antimicrobial proteins, such as lysozyme and lactoferrin, as well as with the complement system in enhancing the killing of bacteria.

[Slide]

This slide is a cartoon which attempts to outline the mechanism of action of pexiganan and the magainins as it is currently understood, and has been published predominantly for the magainins in about 90 publications. I will walk you through this now.

Pexiganan exists as a positively charged linear peptide which has no fixed structure in solution. As it turns out, the external side of the cytoplasmic membrane of bacteria contains an excess of negatively charged phospholipids, predominantly phosphotidal lyserol and cardiolipin. There is electrostatic interaction, it is believed, that occurs between these negatively charged phospholipids, which are not as prominently displayed in mammalian cells, and then after this electrostatic interaction the peptides in the cytoplasmic membrane form an alpha-helical confirmation. About five of these alpha-helices then join together, and extensive physical/chemical work has been done to show this, and form pores in the bacterial membrane that subsequently leads to the lysis of the bacteria.

[Slide]

I will show you an example of the selectivity <u>in vitro</u> that we can show for pexiganan bacterial compared to mammalian cell membranes. In the last month we have learned

with a new series of borane fluorescent labels how to covalently attach a fluorescent label to pexiganan, and have used that here where, with the fluorescent label, we have added pexiganan in solution to a culture of human endothelial cells to which has been added Staph. aureus bacteria. With the addition of Staph. aureus bacteria, you can see in this in vitro experiment that there is selective binding of the fluorescently labeled pexiganan to the bacteria in this mass of mammalian cells.

[Slide]

If we look at electron micrographs of the action of magainins on Gram-negative bacteria -- I will show you the findings here. This is with E. coli. We see here E. coli in closeup view without the addition of magainins. With the addition of the magainins, it is currently believed, though there are not extensive studies on that with Gram-negative bacteria, that there is an initial insertion of the magainins into the outer membrane, probably through interactions with negatively charged lipid A. This then leads to an expansion of the outer membrane, as shown here where you can see it expanded and basically peeled off the E. coli. This happens within a matter of minutes after addition of an inhibitory concentration of magainin. Several minutes later we can see that the bacteria are beginning to undergo lysis.

[Slide]

This then summarizes the preclinical background material that I have shown you. We can say that pexiganan is derived from frog skin peptides and magainins. Both pexiganan and the magainins are members of this larger family of cationic antimicrobial peptides which are commonly used in animals for the defense of epithelial surfaces.

The mechanism of action of pexiganan and the magainins is believed to be pore formation in the cytoplasmic membrane of bacteria and subsequent disruption through this membrane active mechanism of action.

[Slide]

Let's look now at a number of subjects, about the preclinical microbiology and the in vitro activity of pexiganan. In this section we will cover these six topics. I will show you the in vitro spectrum of activity of pexiganan in MIC assays. We will then look for evidence of bactericidal activity in MBC assays. I will show you in vitro cross-resistance studies, that is, looking for activity in vitro of pexiganan against isolates either resistant or susceptible to other antibiotics. I will show you information about in vitro experiments looking for selection or induction of resistant or mutant organisms. We will make some analogies to other cationic antimicrobial agents. Finally, we will look in this section at evidence of

pexiganan's antimicrobial activity in one of our clinical studies in man, the so-called translocated skin flora study.

[Slide]

First, in considering the utility of the spectrum of activity or MIC assays for topical products, I believe it is worth keeping these factors in mind. They do provide information on the relative in vitro activity for the agent against a particular species or isolates. However, they may be difficult to use for the prediction of in vivo microbiological responses. This is because topical antibiotics and pexiganan are typically formulated to a high concentration. For pexiganan it is a one percent formulation; it is 10,000 mcg/mL.

[Slide]

Given these caveats, let's look at the spectrum of activity for MIC assays against a range of organisms. First, staphylococci. This is the first of a series of seven slides where we will look at MIC assays against a range of organisms. I will go over the organization of these slides.

First we show the organism. We have Staph. aureus, Staph. epidermidis, and in this case coagulase-negative staphylococci. We then have the source of the organisms. DFU stands for diabetic foot ulcer. These are the isolates which we got from our two pivotal clinical studies. Non-diabetic foot ulcer isolates are isolates which we collected from a

geographically distributed set of sites across the United States for testing during our preclinical microbiology development program. We then have the number of isolates which have been tested, the MIC values and I will concentrate on the MIC-90 probability value, and then the range of MIC values that have been found.

We will see in general that the sensitivities for diabetic foot ulcer isolates from our clinical trials were similar to those that we collected in our preclinical program. Here we see that for Staph. aureus and coagulase-negative staphylococci the MIC-90 is in the range of 8-16 mcg/mL.

[Slide]

Let's look now at streptococci. We see here that Strep. agalactiae, group B strep., was the third most common isolate from our diabetic foot ulcer patients. The most common was Staph. aureus that we saw on the last slide. Enterococcus faecalis, which we will come to in a moment, was the second most common. We see that for Strep agalactiae and Strep. pyogenes, which was isolated just 11 times from our 835 patients in the studies, the MIC-90 is in the range of 8-16 mcg/mL. Several variants of streptococci are highlighted here because pexiganan has less in vitro activity against them in the concentration of 129-256 mcg/mL. Other streptococci that were tested or isolated at

MIC-90 values are in the range of 16-32.

[Slide]

Let's look now at enterococci. Again, Enterococcus faecalis was the second most common isolate from our diabetic foot ulcer infected patients. The MIC-90 for pexiganan for this organism was 256 mcg/mL in our clinical studies. Enterococcus faecium was occasionally isolated from our diabetic foot ulcer infection patients. The MIC-90 value in our studies was 32 mcg/mL. We have tested for in vitro activity of pexiganan against 10 vancomycin response Enterococcus faecium isolates and the MIC-90 value was 4 mcg/mL, with one isolate having a higher value.

[Slide]

Let's look now at a range of additional Gram-positive aerobes that were isolated from our clinical studies and that can cause potentially skin and subtissue infections. We see that for Corynebacterium, Micrococcus and Aerococcus species the MIC-90 value was 4-8 mcg/mL.

[Slide]

Now on to some Gram-negative aerobes, which we will have two slides on. We see here for Citrobacter, Enterobacter, E. coli and Klebsiella the MIC-90 values were in the range of 8-32 mcg/mL. Against Proteus species, and the most commonly isolated in our clinical studies was Proteus mirabilis, pexiganan has less in vitro activity with

an MIC-90 value greater than 256 mcg/mL. This lesser sensitivity of Proteus genre was also true of the genre Serratia, Morganell_ and Providencia.

[Slide]

Let's look now at some other Gram-negative aerobes. Here we see that for Acinetobacter species, Pseudomonas aeruginosa and other Pseudomonas species and Stenotrophomonas the MIC-90 value ranged from 8-32 mcg/mL. Alcaligenes species were less sensitive in vitro to pexiganan.

[Slide]

Finally, in this series of slides let's look at Gram-positive and Gram-negative anaerobes. We see here that for Bacteroides, Clostridium, Fusobacterium and Peptostreptococcus species Peptostreptococcus was the most common anaerobic isolate in our clinical studies and Prevotella and the MIC-90 values ranged from 4-64 mcg/mL.

[Slide]

Let's look now at evidence of bactericidal activity of pexiganan by comparing the inhibitory to the bactericidal concentrations. This is outlined here. I show you first the Gram-positive organisms that we have studied in these assays, and what we have done is use the NCCLS MIC and MBC assays to compare the difference in doubling dilutions for the bactericidal to the inhibitory

concentration.

You can see that for over 90 percent of the isolates the inhibitory concentration is within two doubling dilutions of the bactericidal concentration -- evidence of excellent bactericidal activity.

[Slide]

This was also true in our in vitro tests of Gram-negative organisms, as outlined here, against a variety of species. Looking at these Gram-negative and Gram-positive isolates that we tested, 288 in total, about 96 percent had the minimum bactericidal concentration within two doubling solutions of the inhibitory concentration.

[Slide]

Let's look now at in vitro activity of pexiganan against isolates which have, by NCCLS criteria or the laboratory criteria from our contractor, Corning SciCor, response to other antibiotic classes. So, again, this will be the in vitro MIC activity ranges.

What I would like to show you here, first for staphylococci, is that if we look at Staph. aureus, coagulase-negative staphylococci or we put them both together it is similar for both against resistant or susceptible, by these criteria, to methicillin, oxacillin or other classes, that for the isolates the MIC-50, MIC-90 value in the ranges are very similar regardless of the

sensitivity or response to these other classes of antibiotics. Really, this could just be an indication that pexiganan is in a unique class of antibiotics compared to these other clinically used antimicrobial agents, as we assess it here in these in vitro studies.

[Slide]

Looking now at Pseudomonas, we see a similar phenomenon for in vitro activity against Pseudomonas species -- resistant or susceptible to imipenem or ciprofloxacin, gentamicin, as well as for Acinetobacter species.

[Slide]

This is also true, finally, for anaerobes as well, where we look at anaerobes resistant or susceptible to Clostridium and Bacteroides species.

[Slide]

We also highlight here that bacteria resistant or susceptible by these in vitro tests do exist in diabetic foot ulcer patients during the 1994-1996 era when we studied them. In general, for Staph. aureus we found by these criteria about 15 percent of the isolates had this in vitro resistance limit, and pexiganan in these in vitro assays has very similar in vitro activity regardless of the susceptibility to these other agents.

[Slide]

Coagulase-negative staphylococci in our patients,

and these are all from our clinical studies, are more commonly outside these limits, and we can see that, again, the in vitro activity of pexiganan, regardless of this, is very similar.

[Slide]

Let's talk for a moment about acquired bacterial resistance against pexiganan and the magainins. First, I would like to point out that we are talking about in vitro tests, looking for mutant organisms or the development of mutant organisms which are more resistant in vitro. It does not refer to clinical resistance or susceptibility in the clinical setting.

We have looked in a number of ways for mutations, as has a number of investigators at the National Institutes of Health, the University of Washington in Seattle and the University of Washington in St. Louis, for mutations which might confer acquired resistance to the magainins and, ourselves, for pexiganan. We have not discovered these to date.

I will show you in a moment some subinhibitory concentration passage studies we have done to see whether there is essentially a high mutation rate which might lead to resistance of the bacteria. We have also done limited chemical and ultraviolet radiation photogenesis studies which have failed to generate resistant isolates for either

Staph. aureus or E. coli. These type of experiments have also been done at the academic centers I outlined for the magainins.

There is no known plasma-mediated resistance for magainins or for other cationic antimicrobial peptides. There are putative mechanisms of intrinsic resistance for magainins which are speculated to be an unattractive outer lipid envelope for Gram-negative bacteria and destructive proteases which have been shown to be produced for Porphyrmonis gingivalis, the gingivitis causing Gram-negative anaerobic bacterium which may cause destruction of the peptide. Again, these are not shown to be transferrable and there is no known plasmid-mediated resistance for cationic antimicrobial peptide.

[Slide]

Let's look at the subinhibitory concentration passage studies which compare pexiganan with several isolates which were previously known to develop increased MICs in vitro with exposure either to mupirocin and fusidic acid. Fusidic acid has been known to have some concerns regarding the development of resistance.

We see here that we take the treatment compound for these ranges of Staph. aureus and Staph. epidermidis isolates and give half inhibitory concentrations of pexiganan over a series of passages. We can see that for

these isolates there was no significant change in the MIC for pexiganan, whereas there is an increase in concentration for mupirocin or the two isolates with fusidic acid, having an increase in MIC values in vitro.

[Slide]

We have done these subinhibitory concentration studies with pexiganan for a variety of isolates. I think it is a total of 31 isolates that are outlined in the briefing document, and I show you here representative data. We see here the isolates that were tested, the initial MIC and then the MIC after 4-7 passes with pexiganan. We see no significant changes which again, I think, indicates that there is no rapid selection of mutants for pexiganan resistance in these in vitro assays.

[Slide]

I would like to make a few comments about resistance development with analogies to other cationic antimicrobial agents. It is true that polymyxin and colistin are cyclic cationic antimicrobial peptides which are derived from Gam-positive bacteria, essentially with activity against Gram-negative bacteria.

I believe that there is a history of limited acquired resistance to these membrane active agents. I believe it is arguable that among the four major classes of antibiotics in clinical use, membrane active agents, cell

wall inhibitors, nucleic acid synthesis inhibitors and protein synthesis inhibitors that, again arguably, the membrane active agents which may also include amphotericin, have the best track record of avoiding the development of resistance, perhaps because it is difficult for microorganisms to change sufficiently their outer surface in toto.

It is also worth considering that animal antimicrobial peptides have been used for millions of years with a high level of expression in the biomass. Though there is diversity among these antimicrobial peptides, they do share certain common features in their mechanism of action, and the introduction of pexiganan into man will probably introduce less of a burden into the environment than, say, the introduction of penicillin compared to the expression of penicillin to penicillium mold in the environment before its introduction. All of these remain speculations and further information will certainly become available with the clinical introduction of pexiganan.

[Slide]

Let's look now at the antimicrobial activity of pexiganan cream in man using the so-called translocated flora technique. What is done here is that a mixed population of bacteria is harvested from the perineal area and then placed onto the forearm underneath the patch.

Underneath that patch then are placed different treatments which included no therapy, placebo containing cream, and then cream containing three increasing concentrations of pexiganan. At time points after the patch is placed, 1, 6 and 24 hours afterwards, we looked at the bacterial colony number expressed as a log of colony forming units per centimeter of skin.

What we found was that with the application of pexiganan cream compared to the placebo cream or no therapy there was about a 3-log or 1000-fold reduction of mixed flora in an hour, which was sustained over the 6-hour period. At the 24-hour period, compared to control, there was still about a 3-log reduction but there was some regrowth beginning of this mixed flora of bacteria.

This is one of the pieces of information, along with in vivo animal studies and ex vivo animal skin studies, that led us to take forward into our pivotal studies one and two percent concentrations of pexiganan, and matching ofloxacin's twice a day dosing, our twice a day dosing schedule which was done during our pivotal clinical studies.

[Slide]

In conclusion of this microbiology section of the presentation, I believe I have shown you that pexiganan has a broad spectrum of activity against a range of Gram-positive and Gram-negative aerobic and anaerobic organisms;

that there is evidence, both from its mechanism of action and from our minimum bactericidal concentration assays, that it has good bactericidal activity.

We have no in vitro cross-resistance to other classes of antimicrobial agents demonstrated. Finally, induction or selection of mutant bacteria that has acquired resistance has not been detected to the limits we have studied it thus far.

[Slide]

Let's turn now to the clinical studies. We will examine here first study design and structure. We will go over the efficacy data and the safety data in detail.

[Slide]

First let's look at some general features. We did two pivotal studies for infected diabetic foot ulcers, enrolled 835 patients. We did these studies with an active control group, which was ofloxacin 400 mg given twice a day, adjusted as appropriate for creatinine clearance.

The studies were done with the so-called double dummy design. That meant that each patient took home a tube of cream and pills. They took either the active ofloxacin pills with placebo cream or the active pexiganan cream with placebo pills in order to ensure blinding. Both were given twice a day, and patient selection was done, as I will show you in more detail in a moment, to study the mild diabetic

foot ulcers as Dr. Lipsky outlined in his classification system.

[Slide]

Our choice of control groups was led by these factors: First, we felt that a placebo group would be unethical to conduct the study because of the risk of progressive infections in these patients. Secondly, there was at the time no approved agent for the specific indication of diabetic foot ulcers. Ofloxacin was approved for the treatment of uncomplicated skin and soft tissue infections caused by Staph. aureus, Strep. pyogenes and Proteus mirabilis, and it had been studied for the treatment, in publications, of complicated skin and soft tissue infections including diabetic foot ulcers. We discussed with the FDA's Division of Anti-Infective Drugs the choice of this control agent, and it was agreed that this would be an appropriate control for our two pivotal studies.

[Slide]

Patient selection is outlined here, where we show you diabetic foot conditions which we excluded from our studies. First, we excluded for this comparison of topical to systemic therapy patients with evidence of osteomyelitis, patients with extensive cellulitis. We had an operational definition for our studies that cellulitis should be within

a 2 cm rim around the ulcer site. Patients with gangrene; patients with evidence of systemic toxicity, whether that be fever or lymphangitis. In general, also most of our patients had minimal or no elevations of their white blood cell count on entering the study. And, they were outpatients that we studied. If inpatient treatment was thought to be required on entering the study, these patients were excluded.

[Slide]

As Dr. Miller and Dr. Lipsky outlined, our diagnosis of infection for these patients was based on the investigator's clinical diagnosis of infection for the diabetic foot ulcer. We also asked them to please document that there was the presence of either purulence or at least two other signs of infection or inflammation on entering the studies. Culture results were taken at baseline and all subsequent visits until cure of the ulcer infection occurred, however, they were not used to establish the diagnosis.

[Slide]

The microbiologic specimen collection and processing for our studies is outlined here. We performed tissue curettage of the base of the ulcer with a scalpel blade after the debridement procedure was performed.

Specimens were then shipped overnight in Port-A-Cul medial to the central laboratory for the study where all

isolations and in vitro susceptibility testing was done, which was Corning SciCor in Indianapolis, Indiana. Cultures were taken at each visit until the patient was clinically cured of infection.

[Slide]

As Dr. Miller and Dr. Lipsky outlined, adjunctive treatment is very important for proper management of all diabetic foot ulcers included infected diabetic foot ulcers. We worked to establish, as much as possible, a uniform inclusion of these adjunctive treatment measures for both of our studies. We did this in two ways for debridement, standard dressing and pressure off-loading through having an investigators meeting for both studies before the studies were begun, and by also producing a video that was sent to each investigator in our pivotal studies which we called, in a bit of a tongue-in-cheek manner, "Frog or Prince," which had actual filming of two debridement procedures and went over the dressing technique and the need for pressure off-loading.

As I will show you in a moment, debridement was performed in about 94 percent of our patients entering the studies. The dressing used for the studies was a dry, non-adherent Owen's dressing placed over the ulcer which was then wrapped with dry gauze. These were then removed carefully twice a day, and it was permissible in the

instructions for the study to put a bit of saline on the non-adherent dressing if there was difficulty in removing it from the ulcer.

Pressure off-loading was done by the investigator's preference. We talked about doing that through crutches, wheelchairs, special shoes, and encouraged the patients not to walk on their bare feet or walk on their feet to a minimal amount.

[Slide]

As I mentioned a moment ago, this outlines for our two studies, which we called study 303 and the second study 304, the percentage of patients which underwent debridement by visits during the study. We can see here the visit and the percentage which underwent debridement for the two treatment groups.

We can see that at the baseline visit about 94 percent of patients entering the study underwent debridement. By the end of the study there was still about 60 percent of patients who were undergoing debridement at their follow-up visit, which was two weeks after the end of treatment, in order to clean any debris from the ulcers.

[Slide]

In our two studies -- again, study MSI-79-303 which we refer to as study 303, and the second study, the 304 study, we enrolled in total 835 patients for the

comparison of pexiganan cream one percent to ofloxacin.

The studies differed materially in only one important way. In study 303 there was a planned interim analysis. In the early part of study 303 before this planned interim analysis there was a third treatment arm which was pexiganan cream two percent. At the planned interim analysis, which took place after about 65 patients had been enrolled in the 3 treatment groups, we saw no difference in the clinical response at day 10 for the 3 treatments, all over 90 percent, and therefore moved ahead with the rest of the study comparing pexiganan cream one percent to ofloxacin, with the two percent arm dropped. The one percent cream was then carried forward as the only pexiganan concentration studied in our second study.

[Slide]

The time points for our therapy and the assessments are outlined here. Patients received therapy for 14 to 28 days at the discretion of the investigator. Essentially, if the investigator felt that the ulcer infection was cured after 14 days therapy could be stopped at that visit. If they felt that the patient was not cured at that visit and wished to continue on with the antimicrobial therapy, it could be conducted out to 28 days.

Assessment timing during the study is outlined here. Patients were followed carefully with the baseline

visit followed by assessments at which data was collected at days 3, 10 and 14 and day 21 if therapy had not already been stopped. But recall that in many data analyses you will see the end of treatment visit and that, again, varied from 14 to 28 days and finally the follow-up visit which took place 2 weeks after the end of treatment visit.

So, in summary, these patients in general received 2-4 weeks of therapy and they were seen, depending on the length of therapy, 4 to 6 weeks afterwards.

[Slide]

Let's look at the demographics of whom we studied. This is outlined for us for the 303 study, where we outline the demographics related to gender, ethnicity, weight and age for pexiganan and ofloxacin and for the total for this study.

We can see here that about 75 percent of the individuals enrolling into the study were male. Diabetic foot ulcers are known to be slightly more common in men than in women. We also had a number of Veterans Administration sites participating, particularly in this study.

Ethnicity is shown here where the patients were predominantly white, with representation of African-American and other ethnic groups. The patients tended to be slightly overweight, and their average age was about 60.

[Slide]

The demographics were very similar in the 304 study. There were slightly less males compared to females in this study. The ethnicity was similar. The patients were again slightly overweight, and the average age was about 60. Both studies were well matched between the two treatment groups.

[Slide]

As Dr. Miller and Dr. Lipsky outlined, the pathogenic etiology of the diabetic foot ulcer needs to be considered, and this slide shows for our 303 study that the groups were well matched for the presence of gross vascular disease. We see that about 10 percent of people entering the studies had absence of a palpable dorsal pedis or posteriad tibial pulse.

Patients were not excluded from participating in the study because of gross vascular disease. If the patient had symptomatic peripheral vascular disease or if there was asymptomatic disease with a Doppler pulse pressure of less than 40 mm Hg, the patient was referred to a vascular surgeon. If the vascular surgeon felt that conservative therapy was indicated the patient was enrolled in the studies.

We can see that this degree of critical ischemia or this degree of gross vascular disease was present in about 2 percent of our patients. In contrast, over 85

percent of the patients in our study had evidence of peripheral neuropathy, which was assessed both by a nylon monofilament which gives 10 gm of pressure, a common semi-quantitative way of assessing the degree of peripheral neuropathy sensation, and by tuning fork and other clinical exams.

These findings were similar in the second study, again well matched between the two groups, with non-palpable pulses present in 10-15 percent and neuropathy in over 80 percent.

[Slide]

Let's look now at the history that we captured in our studies of prior foot ulcers, prior osteomyelitis or prior amputations, all of which are features of individuals which can have previous foot ulcers because of the chronic nature of the neuropathy in diabetic disease.

[Slide]

We will come back to that in a moment. I will just outline here briefly that in addition most patients in our studies, with the multi-systemic complications of long-standing diabetes, were on multiple medications. Almost all patients were on at least some medication, and the mean number of medications in the two studies was 5-6 that the patients were on. About two-thirds of the patients entering our studies took insulin therapy for their diabetes and

about one-third took oral agents, and a few took both.

[Slide]

Let's look now at these histories of prior episodes related to diabetic foot ulcer infections for our patients entering the studies. We can see here that about two-thirds of individuals entering the studies, 303 and 304, had a prior history of a diabetic foot ulcer. We can see that the prior history of osteomyelitis -- and again, this is not osteomyelitis on entering the study but a history of osteomyelitis -- occurred in about one-third to one-fifth of patients entering the study. The history was most common for patients in the pexiganan 303 study treatment group, and the difference in these rates of osteomyelitis history had a significant p value.

Regarding a history of amputations and foot surgery, which is what we captured on our case report forms, we can see that there was a significant excess of patients with a prior history of amputation or foot infection surgery in the pexiganan 303 study group. Again, this was a significant difference compared to the ofloxacin treatment group.

We can see that in the 304 study there was a slight excess of patients with a history of amputation or foot surgery in the pexiganan treatment group.

What we did further, after the study was

concluded, was to look at how many of the patients, with the best information we had, that had this history of amputation and foot surgery had actually a history of amputation. This was also reported on the case report form by the specific surgical procedure that had been performed previously. We see that in particular there was an excess of this amputation history in the pexiganan patients in study 303 compared to the ofloxacin patients in 303 or compared to the history of amputation among either treatment group in the 304 study.

This may have some bearing on the interpretation of the clinical outcome for these studies. So, it certainly remains speculative, and we will return to that a bit later.

[Slide]

Let's look now at the efficacy data.

[Slide]

What I would like to do first is just outline the history of the statistical analysis plans for these studies from the protocol up to the submission of the new drug application. In the original protocols the primary outcome was considered to be clinical outcome at day 10 in an evaluable population. I believe that day 10 was of interest to the company because ofloxacin was approved for 10 days of therapy at that time. A secondary outcome was microbiological outcome.

In our prospective statistical plan for the interim analysis of study 303 the primary outcome was the clinical outcome at day 10 in an evaluable population. We had our prospective statistical plan for study 303 where our primary clinical outcome was listed to be clinical outcome at day 10 in the intent-to-treat population. This was submitted and reviewed in a teleconference with the Division of Anti-Infective Drugs before breaking the blind. We had a similar plan for study 304, and at that time the agency let us know that they would prefer to place emphasis on the follow-up time point.

In our final statistical plan, submitted before the submission of the NDA, we did detail the criteria for two per-protocol populations for which you will see data analysis today.

[Slide]

Over the time period for the preparation of the NDA we worked with the Division of Anti-Infective Drug Products and, from written communications and from oral communications with them, we believe that they were interested in having us submit in the NDA, which we did, as well as in the briefing document, the primary outcomes being related to clinical outcome, microbiological outcome and the combination of the two -- therapeutic response.

We would agree that consistently and in the

statistical plans we have outline clinical outcome as the primary population, and I just wanted to spend a few seconds explaining how we submitted our NDA and briefing document with these listed as primary outcomes.

Our secondary outcome submitted in the NDA and the briefing outcome, for which I will present the data to you today, related to the wound scoring systems, of which there were two, and the measurements of the ulcers as they improved during the study, as well as the eradication of baseline pathogens by organism. Our microbiological outcome here is on a per-subject basis, and I will explain that more in a few moments.

[Slide]

Our principal time points of interest, for which I will show you some data, relate to the interest in the development of the studies for the day 10 visit, the end of treatment visit and finally the follow-up visit, which again was two weeks after the end of treatment.

[Slide]

We have analyzed in the submission and your briefing document 10 different populations from these studies. Our purpose was to work with the division to examine a range of potential biases that different subpopulations may help elucidate compared to the intent-to-treat population. We will show you evidence that in general

there is a consistent set of results across these different populations.

[Slide]

In our presentation today and in meeting with the division in February in planning this meeting, we discussed that we would plan to present today for clinical outcome the intent-to-treat population and, second, per-protocol 2 population which is intent-to-treat patients which have none of the nine protocol violations which are outlined in the briefing document.

For microbiological outcome and therapeutic response we looked only at patients which had a positive culture at the baseline visit and correspond to these two other populations.

For our two studies, about 80 percent of the patients enrolled in the study had positive cultures of the tissue curettage samples taken after debridement of the ulcer at the baseline visit. So, we will have these four populations in our presentation, intent-to-treat, the per-protocol 2 for clinical outcome, and their microbiological counterparts, and microbiological outcome is taken into account for these two parameters.

In preparing our presentation, we discussed with the agency that we would give complementary presentations where we would both have information about the intent-to-

treat and intent-to-treat microbiological population. We will present the two per-protocol populations which differ in one area, which is the method of assessment of compliance to the therapies. It is a bit of a challenge to assess the compliance of a topical and an oral therapy together in the same trial, and I will outline for you in a moment the two ways that we did this in collecting data during our protocols.

In addition, the FDA, as they have outlined for you in their background materials, has analyzed an eleventh population which is the per-protocol population based on the per-protocol 1 population, and they have looked at this in the 303 study only. The difference here is that this population places an emphasis on coming back for the follow-up visit around a tighter visit window. Magainin did not use the follow-up visit window for our two per-protocol populations. We used visit windows at the end of treatment and day 10.

So, having said all that, I will be glad to explain that further, as much as people would like, but I think in summary, we will show you the data and I would be happy to answer any questions about how they relate to each other.

[Slide]

Just to spend one more moment on these two per-

protocol populations which just differ in the method of compliance assessment, in comparing a pill and a topical therapy what we did in the protocol was assess compliance in two ways. One was by doing an actual pill count of the ofloxacin taken. We did not try, for example, to weigh the tubes of the topical agent because of potential differences in ulcer size and potentially patients would apply it slightly differently. So, we did not try to assess compliance based on that way. Instead, for the pill and the cream together we asked the investigators to interview the patients and ask them, and form an opinion on had they been compliant with the therapy at least 75 percent of the time for both.

So, in per-protocol 1 the only difference is that it relies on a pill count and it uses the pill count compliance percentage, 60 percent of the pill count that has been taken that we outlined in our prospective statistical plan. In contrast, the per-protocol 2 includes patients where there was evidence of compliance with both treatments as assessed by the investigator, and uses the 75 percent limit that the investigators assessed during the original protocol.

[Slide]

Let's look now at the data.

[Slide]

First, clinical outcome. At the follow-up and end of treatment visits clinical outcome was asked to be placed into one of these three categories by the investigators. The patients were rated either as cured, which was defined as no further signs or symptoms of infection; improved, which was defined as significant improvement but incompletely resolved; or failed, no apparent response to therapy.

In analyzing the results of clinical outcome we can have the data put together into so-called clinical responders, which is commonly done for anti-infective products which includes patients who are rated as cured and improved together compared to patients who are non-responders, who failed. I will also show you data breaking out the cured and improved patients so you can get a feel for how commonly patients were cured at the time points in the study.

[Slide]

Let's look first at this slide which outlines the type of data presentation that you will see repeatedly for clinical outcome, microbiological outcome and therapeutic response. The slide is set up in this way: First we have the population in the study that we are talking about. Here is study 303, study 304, and for clinical outcome the intent-to-treat and per-protocol 2 populations. We then have a listing for you of the number and percentage of individuals

who were responders to clinical outcome -- again, people who were cured plus people who were improved. We have that for each population with the percentages for both indications, pexiganan and ofloxacin. In the right-hand column we have the 95 percent confidence interval of the difference in percentages calculated exactly between the two therapies.

We see here that at day 10 there was 84 percent response in study 303 for pexiganan and 89 percent in study 304. For ofloxacin the range in the two studies is 88-90 percent. The confidence interval limits are shown here. They all cross zero, meaning that the p value is greater than 0.05, and they are all within 15 percent of the lower bound of the confidence limit.

[Slide]

Let's look now at end of treatment after 2-4 weeks of treatment. We see that for study 303 and here for the intent-to-treat for per-protocol 2 populations for study 304, the percentage of individuals who had clinical response. We see that in study 303 in the two populations pexiganan had an 85 percent response rate and ofloxacin a 91 percent response rate. We see that the 95 percent confidence interval, the difference, does not cross zero for the intent-to-treat population. At end of treatment in the per-protocol 2 population it does cross zero and the lower bound is within 15 percent.

In study 304 we have pexiganan response rates of 89 and 91 percent, and similar for ofloxacin, with confidence intervals evenly straddling zero.

[Slide]

Let's look now at the follow-up visit. We see here that in study 303 pexiganan's clinical response rate is 75-77 percent. For ofloxacin it is 84 percent for the two populations. The 95 percent confidence interval does not cross zero; it is within 15 percent. In the per-protocol 2 group it does slightly cross zero and is beyond the 15 percent limit for the confidence interval on the down side.

In study 304 we have 82-83 percent response for pexiganan and 84-86 percent response for ofloxacin. The confidence intervals are shown.

Let's look now at patients who were cured and improved. What I will show you is that at the day 10 visit some patients are cured, more are improved, and at the end of treatment and follow-up visits more patients are cured than improved. We will look at that in just a moment.

[Slide]

At day 10, and I show this slide for several reasons -- to show the consistency of the results across the populations. We see for study 303 and for study 304 for pexiganan and ofloxacin the percentage of patients for clinical response, either cured or improved. We see that for

these 6 populations.

We can see that in general the percentage of cures for both pexiganan and ofloxacin at day 10 was higher in study 303 than it was in study 304 by about 5-10 percent. In addition, we can see that the results are consistent across the populations and that it was most common at the day 10 time point for patients to be improved but not cured.

[Slide]

Let's look now at end of treatment. We can see that the percentage of cures compared to day 10, which was on average about 22 days of therapy for each treatment -- at this time point we see that the percentage of cures is again slightly higher for both study treatments in the 303 study than in the 304 study. In general, the percentage of cures in the 303 study is slightly higher for ofloxacin than pexiganan. They are fairly well matched, with perhaps a small difference in favor of pexiganan for some populations in the 304 study for the percentage of cures.

In general, we see again at this later time point that the percentage of individuals that were improved was about 10 percent less in the 303 study with the higher percentage of cures than it was in the 304 study, but this higher percentage of improved. This may suggest that there was a somewhat different population of patients that we were studying in these two studies, the 303 and the 304 study

but, of course, that remains speculative.

[Slide]

At follow-up we see that in general the percentage of cures has moved up slightly compared to the end of treatment time point, and the percentage of improved patients has decreased compared to the end of treatment time point for both studies, again with a lower percentage of improved in study 303 than in 304 and a higher percentage of cures in study 303 than in 304.

[Slide]

Let's look now at this category of per-subject microbiological outcome. We divide this microbiological outcome on the per-subject basis into the eight categories outlined here. What I would like to do for just a moment is just walk you through an example of an isolation of three bacteria from an ulcer at the beginning of the study, and explain to you how people fall into the different categories.

If a patient has three organisms grow out of the ulcer culture at the beginning of the study and at the assessment for microbiological outcome, all three of those organisms are gone and no new organisms have grown out, we call that infection resolved.

For infection improved it would be a situation where one or two of the organisms present at the beginning

of the study are gone and, again, no new organisms have grown out.

Treatment failure refers to the situation where all three organisms remain at the end of the study and no new organisms have grown out.

Colonization refers to the situation where any new organism has grown out during the study and the patient is either cured or improved clinically.

Superinfection -- there are new organisms and the patient is a treatment failure.

For unevaluable patients there was no tissue curettage taken, most commonly because the patient had improved and the investigator did not perform it.

Finally, relapse and reinfection occurred rarely. They refer to situations where the patient did worse clinically between end of treatment and follow-up and there were either new or the same organisms growing out.

[Slide]

So having gone through that, let's now look first at how it broke out into the different categories for the two studies to give you some perspective on that, and the complexities.

We will look at the data first broken down into the different categories, and the statistical analysis was performed on patients who were responders, that is, their

infection resolved and their infection has improved. In all cases, no new organisms were grown out of the ulcer at the end of treatment or follow-up visit, and either all the organisms present at baseline are gone or some of them are gone. All other categories we will call non-responders, including colonization.

[Slide]

So broken down, what I would like to show you on this slide that looks at study 303 are these microbiological response categories among the intent-to-treat microbiological population, roughly the 80 percent of people entering the studies who had positive cultures at their baseline visit. We see that the most common response, occurring in about 40 percent of patients, was infection resolved.

We see that the second most common response category was colonization where new organisms are grown out but the patient was either improved or cured clinically. You can see that treatment failures microbiologically were relatively an uncommon category, and that the third largest category, particularly in this study at the follow-up visit, was patients who did not have tissue curettage samples performed by the investigator or, in a few cases, the cultures were not processed sufficiently or not received by the laboratory. That occurred very rarely.

[Slide]

In 304 there is a similar phenomenon where about 40 percent of the patients, slightly higher in the ofloxacin treatment group in the follow-up visit, had infection resolved, again, the most common category.

Treatment failure again was relatively uncommon, as actually was infection improved. Again, the second most common category was colonization.

[Slide]

Let's look now at the data classified into responders, resolved and improved, versus non-responders. Let's look first at the day 10 visit where we can see that for study 303 and 304 for these positive culture, intent-to-treat and per-protocol 2 populations the pexiganan response rates for the two studies ranged from 32-42 percent and for ofloxacin from 21-37 percent across these populations. The confidence intervals for the difference is shown here, and we can see that in the 304 study at the day 10 time point for this overall per-subject microbiological outcome there was a preference in favor of pexiganan.

[Slide]

At the end of treatment time point, outlined here, we can see again the two positive culture baseline populations. We can see that in the 303 study for the two populations the overall microbiological outcome at end of

treatment was 48-53 percent for pexiganan, 47-48 percent for ofloxacin. The confidence intervals well straddle zero. In study 304 we had a similar finding for overall microbiological outcome at end of treatment, with pexiganan 46-51 percent and ofloxacin 47-52 percent. Again, the confidence intervals well straddle zero.

[Slide]

For study 304 and 303 at follow-up, the overall microbiological outcome data is outlined here. We see here that in study 303 the point estimates for pexiganan for the overall microbiological response were 42-45 percent, for ofloxacin 46 and 45 percent for these two populations. In study 304 it was 46-51 percent for pexiganan and 47 and 52 percent for ofloxacin. So, consistently for per-subject overall microbiological outcome I believe there were equivalent responses across the two studies at the time points outlined, but perhaps a slight favoring early on in the study for pexiganan in study 304.

[Slide]

Let's look now at the category of therapeutic response which is outlined here for the percentage of patients for both clinically cured and microbiologically resolved of their organisms with no new organisms growing out. We can see that in study 303 in the intent-to-treat and per-protocol 2 populations with positive cultures for

pexiganan the percentages are 35 and 40 percent, for ofloxacin 38 and 42 percent. The confidence intervals well straddle zero. In study 304 we can see that the percentage of both clinical and microbiological cures was by the point estimate slightly lower for pexiganan at end of treatment than for ofloxacin, with the confidence intervals still being significantly above zero but below 15 percent for both populations.

[Slide]

Regarding the therapeutic response at follow-up as outlined here, for pexiganan we have 39 percent, for ofloxacin 41 percent in the 303 study, again well straddling zero for the confidence interval, and the point estimates for the therapeutic response, the clinical and microbiological cure in study 304 were lower for pexiganan than for ofloxacin, and I believe that the confidence interval on these populations, even though it crosses zero and the p value is greater than 0.05, certainly the lower bound goes below 15 and actually 20 percent for the per-protocol 2 group, with much fewer patients which can widen the confidence interval.

[Slide]

So looking at all this data on the clinical and microbiological and therapeutic responses, I would like to make these observations: First, that we saw high rates of

clinical response for both treatments in the studies at day 10, at the end of treatment where it was 85-91 percent for pexiganan and 89-91 percent for ofloxacin in the data that I showed you, and at follow-up 75-83 percent for pexiganan and 84-86 percent for ofloxacin.

In general, we frequently had a good clinical response without microbial sterilization, which may be due to these patients having foot infections in a patient with diabetes where skin colonization can be more common, and the difficulty in sterilizing the skin in general.

[Slide]

In terms of these efficacy data for clinical, microbiological outcome and therapeutic response, for study 303 I would summarize that we showed you that pexiganan cream was equivalent to ofloxacin for subject microbiological outcome and for therapeutic response. For clinical outcome, particularly at the follow-up visit, we did not stay within, either crossing zero or in the case of the other population going below 15 percent for the 95 percent difference in the confidence interval.

For the 304 study we were equivalent for microbiological outcome and clinical outcome. Therapeutic response, even though it crossed zero, did go below in the per-protocol 2 population, minus 20 percent.

[Slide]

Let's talk for a moment about these pexiganan clinical response rates compared to ofloxacin in studies 303 and 304. In general, if we look at the pexiganan clinical response rate between the two studies, they can be considered potentially comparable to each other because they are within each other's confidence intervals, but they were lower in the 303 study than in the 304 study. It is worth keeping in mind that for both studies we saw this equivalent per-subject microbiological response.

The clinical response is really the investigator's assessment of the resolution or significant improvement of signs and symptoms of infection. These factors -- these signs and symptoms of infection may be contributed to by a number of conditions other than colonization or infection with microbes.

It is worth considering that we did have two historical host potential severity factors, as Dr. Lipsky had particularly outlined, regarding the history of amputation that were more common in the pexiganan compared to ofloxacin treatment group in study 303. In particular, there was a significant difference for enrollment of patients with a history of amputation in study 303 in the pexiganan group compared to the ofloxacin treatment group, and there was a marginally statistically significant history of patients in the 303 pexiganan group having a previous

history of osteomyelitis.

[Slide]

We looked on an exploratory basis at a number of covariates that we wondered potentially, on a kind of simplistic analysis, did they have this covariate or not, even though it is obviously very complex, and one other one that I mentioned to you in the briefing document that we have been intrigued by but don't fully understand is that at the end of treatment we found that males had a lower clinical response rate than females by about 20 percent. The difference was not as dramatic or didn't exist in some populations at follow-up, but it was true that this difference between male and female clinical response was about 10 percent at end of treatment for both the 303 and the 304 study.

We also would like to point out that we did two measures where we believe we have shown equivalence for the populations of secondary clinical outcomes of wound scores and wound infection scores, which are semi-quantitative measures of these signs and symptoms of infection, and it is potentially interesting to talk about how these may correlate with the investigator's assessment.

[Slide]

So having said that, let's now move on and show you the data about these secondary endpoints of wound

assessment and baseline pathogen eradication.

[Slide]

First regarding wound assessments, we used two wound scoring systems. The first is the total wound score. This had been published in the literature by Drs. Knighton and Pecarraro. It has the following features: It has signs and symptoms of infection. The specific ones are outlined here. It assesses peripheral pulses, and it assesses wound measurements of variant depth and, as a positive feature, increasing granulation tissue.

Since peripheral pulses should not and did not change during the study to any significant degree, this score and its improvement during the study is essentially a combination of signs and symptoms of infection and wound measurement. Duration of the ulcer is also a factor in this score. Our patient's ulcers had a duration entering the study of a median value of about three months.

[Slide]

The wound infection score -- we worked with Dr. Pecarraro and Dr. Lipsky to develop this score for our pivotal studies. It had not been previously published. The score gives individual scores from 0-3 which are assigned to seven parameters of wound inflammation, which are outlined here.

In addition to this wound infection score, we made

two types of measurements of the wound. We looked at wound area, which was done by computerized planimetry of an actual wound tracing taken after debridement, and wound depth, which was done by insertion of a probe and then measuring the depth of the probe inserted into the ulcer. This was commonly done with a Q-tip and was reported directly by the investigator.

[Slide]

Just to give you an idea of how these assessments broke down between the two treatments for the two studies, I have that outlined here. The total wound score has a range of values from 3-80, and we can see that the values were well matched, slightly greater for pexiganan but not significantly so in the 303 study.

They were also well matched for wound infection score. For wound area there was a slight increase in the median wound area value entering the study. They were well matched for wound depth. These were, in general, superficial diabetic foot ulcers.

[Slide]

In study 304 we see again that the two treatment groups, pexiganan and ofloxacin, were well matched for wound score and wound infection score. Wound area was marginally larger for ofloxacin for the median in this study, and well matched for wound depth.

[Slide]

Let's look now at a plot of mean change in this total wound score over time in the study for the intent-to-treat group. This is for study 303, and we will see a number of graphs of this nature.

On the Y axis we will look for the change from the baseline value for the wound score and for the other wound parameters. So, at baseline the values here shows the improvement in wound score units. This has been looked at for the visits during the study. Pexiganan is outlined in yellow and ofloxacin in white.

We can see that for study 303 this total wound score assessment of signs and symptoms of infection and wound measurements shows a similar improvement over the course of the study for pexiganan and ofloxacin.

[Slide]

Let's look now at study 304 for the mean change in the total wound score over time. We can see again that during the course of the study there is improvement for both pexiganan and ofloxacin, and that the improvement is very similar.

[Slide]

Let's look now at the wound infection scoring system. For the wound infection score, we can see here the improvement score units. Again, it began around the 7 range

for both treatments over the visits during the study. We can see that across the population for patients treated with pexiganan or ofloxacin there is a marginally greater decrease for the mean change in wound infection score over time which is equivalent and overlapping both at the end of treatment and follow-up visits.

[Slide]

This is similar in study 304 where we see again that there is a marginally greater decrease in the wound infection score for ofloxacin over the time course of the study, and that these are overlapping at follow-up and barely overlapping, but they are, at the end of treatment.

[Slide]

How about median change in wound area over time? Wound area, which is related to wound healing, is treated for uninfected diabetic foot ulcers with debridement, pressure off-loading and good dressing care techniques that Dr. Miller outlined. In assessing wound area for antimicrobial agents, it is important to keep in mind that this could be influenced by such factors as debridement which, as I showed you was still occurring commonly in the patients during the study through the follow-up visit.

Here I show you the change in baseline in the wound area in millimeters squared across the visits for the study for pexiganan and ofloxacin. This is plotted in the

following way, the central values, or the mean, or 50th percentile of improvement. The upper bars are the 25th percentile of improvement and the lower bars are the 75th percentile of improvement for pexiganan and ofloxacin in the 303 study. We can see that these look very similar.

[Slide]

Let's look now at the 304 study. We see here that in the 304 study for the median change in wound area over time there is a slight increase in the improvement in wound area for ofloxacin compared to pexiganan, which for the median change is about minus 60 mm^2 improvement for pexiganan and about 90 mm^2 improvement for ofloxacin at the follow-up visit. You can see also that ofloxacin is favored for improvement in this median wound area for the 25th and 75th percentile of improvement. Again the improvements are in the order or about 30 mm^2 greater.

Now, wound area could be assessed by a number of methods: You could look at the median; you could look at the mean; you could look at the percentage improvement, either the mean percentage improvement or the median percentage improvement. I will show you data for your reference and potentially for your discussions today, if you would like, of the data broken down in this way for end of treatment and follow-up and including how it looked for patients who were either cured, improved or failed. I will show you that there

was significantly better wound improvement for both treatments among patients who were cured and among patients who were improved, and that ofloxacin in general there was less correlation with improvement in the wound area with the clinical response than for pexiganan.

Most of the difference in the wound area between pexiganan and ofloxacin occur, particularly in the 303 study, as I will show you now, among patients who failed in their clinical response.

[Slide]

So, if we look here, I have outlined for you at the end of treatment and at follow-up the type of analysis of wound area improvement, mean, median, median probability, and mean percent for patients that are cured, improved and failed.

You can look over these numbers, and I think what you will see is that in particular among patients who were failed, and these patients were frequently undergoing debridement. I have it broken down that way also for those who have interest This was the group where there was in particular, particularly at the end of treatment, a greater decrease in the wound area compared to pexiganan. In some cases in the cured and improved group pexiganan was slightly favored.

In general, the mean percentage of reduction in

wound area at follow-up for pexiganan and ofloxacin was 62 percent for pexiganan and 69 percent for ofloxacin. For median improvement it was about 85 percent. So, patients were in general having great improvements in their ulcer area among the 50 percent, 55 percent who were cured.

[Slide]

For the 304 study similar data analysis is outlined here. We can see that among patients that are cured by a number of measures of the absolute wound area, particularly for the mean, ofloxacin is favored. It is also favored slightly for the median. You can see again that the median percentage of improvement for both treatments at follow-up is very high among the 50 percent or so of patients who were cured. It is in general lower for patients in both treatments who are improved. Again, there is this phenomenon, particularly here at end of treatment and follow-up, where there was a favoring of ofloxacin for wound improvement among patients who were clinically failed. I think this shows some of the complexities in considering the impact of antimicrobial therapy on wound improvement measures.

[Slide]

We look now briefly at wound assessments at the wound depth. We see improvements in the wound depth, which again began at about 3 mm median depth over the course of

the study in the 25th and 75th percentile of improvement.

[Slide]

I have similar data for the 304 study, where we see a similar type of curve where for both treatments there is improvement in wound depth over the course of the study. The median, the 25th and the 75th percentile of improvement are shown.

[Slide]

Having covered these wound assessments, let's now look at the eradication data during the studies.

[Slide]

First, let's define for you our baseline pathogen criteria. In the analyses that I will show you on organism eradication during the study, I would like to point out that if cultures were done which were viridans streptococci, corynebacteria, Bacillus species or Propionibacterium species, these were excluded from the analysis as baseline pathogens unless they were present in pure culture.

Coagulase-negative staphylococci was commonly Staphylococcus epidermidis, and was excluded unless there was 3-plus or 4-plus growth on this semi-quantitative scale of 1-plus to 4-plus growth. If there was this growth, it was considered a baseline pathogen for the analysis. If there was lighter growth it was not.

DR. CRAIG: How much time do you have left?

DR. HOLROYD: Dr. Craig, I think about 15 minutes, sir.

DR. CRAIG: You are already 10 minutes over the allotted time.

DR. HOLROYD: Thank you. I apologize. I will move on.

[Slide]

So, we see here that for total pathogens present at baseline and eradicated at follow-up, it was 66 percent and 69 percent for pexiganan and ofloxacin, 62 percent and 66 percent for all pathogens in the studies.

[Slide]

If we break this down now by organisms, we see in study 303 that among these organisms here, from most common to less common isolates -- and goes on down to about 100 different species -- among Staphylococcus aureus and Streptococcus agalactiae isolates there was less commonly eradication for pexiganan slightly more often than for ofloxacin.

[Slide]

In study 304 we see that among the three most common isolates, Staph. aureus, Enterococcus faecalis and Strep. agalactiae, there was slightly less common eradication of these isolates in the ulcers for pexiganan than for ofloxacin. There also was a slight difference, but

the numbers are much less, for Proteus mirabilis, as we see here, compared to ofloxacin.

[Slide]

If we look at evidence of colonization that may be going on in these ulcers, what we have done here is take the Staph. aureus isolates of people that had Staph. aureus at their baseline visit and had Staph. aureus at their follow-up visit.

Let's look at the cultures of these ulcers and see if there has been a significant change in the MIC value for the number for these isolates that are in the ulcers at follow-up compared to what was there in the beginning. If one could consider that a 2-fold dilution or greater difference in the MIC value may indicate that there is a different predominance of organisms in the ulcer, what I show here is that both for the pexiganan and ofloxacin treatment group there is certainly a fair percentage of isolates which have a significant difference in the MIC values at the beginning and end of the study for staph. This may be evidence suggestive of colonization occurring of these ulcers. Again, it does not address the potential turnover of ulcers within this group where there is no significant change in the MIC value.

[Slide]

We see this similar phenomenon occurring if we

look at oxacillin MICs to Staph. aureus at the beginning or the end of the study for both treatment groups, with a good number of isolates on a percentage basis having fairly large changes.

[Slide]

Another phenomenon can be see here in the ofloxacin MICs for Staph. aureus. We see that in the pexiganan treatment group where there has been no pressure with ofloxacin during the treatment period there are more commonly isolates at the end of the study which have values close to their baseline. In contrast, in the ofloxacin treatment group exposed to ofloxacin you can see that toward the end of the study there are a number of isolates which have increased MIC values compared to the beginning of the study. Perhaps they are colonized with these isolates against which ofloxacin has less activity in vitro.

[Slide]

So in summarizing our secondary efficacy endpoint data, I have shown you that the wound improvement data, I believe, is similar; that total pathogens eradicated at follow-up are similar; and that eradication rates for pexiganan are slightly lower for some common Gram-positive isolates. I would ask you to consider whether colonization might reasonably be more common with local therapy as systemic therapy with ofloxacin may decrease colonization on

the rest of the skin and, in the case of Staph. aureus potentially decrease nasal colonization compared to our local therapy.

[Slide]

Let's look now at the safety data.

[Slide]

Pexiganan has been given to 1335 individuals including 496 in our clinical pharmacology studies, and the concentrations have ranged from 0.5 percent to 2 percent.

[Slide]

In earlier human studies outlined here, we showed in 27 subjects, compared to vehicle cream of petrolatum, that both the vehicle and pexiganan had negligible irritation. We also did a study showing that they have no phototoxicity.

We have done three studies looking at the so-called maximization protocol which we believe assesses sensitization potential. We have shown that there is minimal to mild skin sensitization potential for pexiganan in these studies. In the largest of the studies, which included over 200 subjects, the investigator's conclusion was that there was no evidence of skin sensitization for pexiganan. However, there was a slight increase in the number of local increases of erythema at the patch site. I could talk more about this in a moment but will say that in these skin

maximization assays which outline skin sensitization potential reviews by dermatologists such as Dr. Jim Leyden point out that benzoyl peroxide, used over-the-counter to treat acne, has about an 80 percent rate of contact allergy in these assays yet is used safely, whereas clonidine patches have a 1-2 percent incidence in this assay but have about a 20 percent incidence in clinical use. I believe I will show you that pexiganan has an excellent cutaneous profile.

[Slide]

We submitted, with the FDA's discussion, a waiver for human pharmacokinetic studies based on our animal absorption data and the margin of safety we saw in animals, assuming even 100 percent absorption in man.

[Slide]

The extent of exposure with the studies was the same, as you can see, for ofloxacin and pexiganan and the length of therapy wasn't really different during the time points in the study, with each group getting about 3 weeks of therapy.

[Slide]

If we look in this oral versus topical treatment group at what adverse events were considered probably related, and the investigators were blinded when they made this assessment and knew there was a 50 percent chance the

patient could be on oral ofloxacin, we see that in general there were very few adverse events rated by the investigators as probably related to either study medication. Most were non-specific, including diarrhea, headache, pain and nausea. One difference was in 6 patients taking ofloxacin where insomnia was felt to be probably related, and insomnia is a known side effect of ofloxacin.

[Slide]

If we look at the most frequent side effects, regardless of study medication, during the studies, combined here for 303 and 304, we can see them outlined here in decreasing incidence for pexiganan. We can see that the most common was diarrhea. Cellulitis was slightly more common in the pexiganan group than in the ofloxacin treatment group. Osteomyelitis was slightly more common in the ofloxacin than the pexiganan group. Others of note were insomnia, which occurred 6 percent of the time in the ofloxacin group and less than 1 percent in the pexiganan group. Accidental injury, which included mostly lacerations and minor injuries, was slightly more common in the ofloxacin group. Overall, there were about 4 percent fewer patients reporting at least one adverse event among these individuals with advanced diabetes in the pexiganan group.

DR. CRAIG: You have five minutes to finish up.

DR. HOLROYD: Thank you, Dr. Craig. Thank you for

the indulgence. I appreciate it.

[Slide]

Cutaneous adverse event profiles are very similar for the two study medications.

[Slide]

Regarding serious adverse events, there was more commonly severe cellulitis in the pexiganan patients, severe osteomyelitis in the ofloxacin patients. The numbers are outlined for the two studies.

[Slide]

The point here of adverse events leading to withdrawal, cellulitis was more common in the pexiganan patients. Infection and osteomyelitis were about evenly matched.

[Slide]

Regarding severe or life-threatening adverse events, cellulitis was more commonly severe in the pexiganan patients; osteomyelitis and ulcer infection were commonly severe in the ofloxacin patients.

[Slide]

Regarding the consequences of being a treatment failure, most patients went through the treatment follow-up period off antibiotics even if they were considered clinically a failure. We can see that about 30 percent went on antibiotics during the follow-up period.

[Slide]

We can see that patients that weren't placed on antibiotics occasionally improved or were cured as rated by the investigator. These were all considered failures for the data analysis.

[Slide]

We can see that more patients went into the hospital for pexiganan in 303 in this period and that more, either the end of treatment or failures, went into the hospital in the ofloxacin group in study 304.

[Slide]

Amputation for 11 and 9; 42 percent of the patients had a history of prior amputation or foot surgery. There were 2 transmetatarsal and 1 below the knee amputations in the ofloxacin group. One partial transmetatarsal in the pexiganan group.

[Slide]

There were 5 deaths, and there were 2 in the pexiganan and 3 in the ofloxacin group. All were cardiovascular related after treatment medications were stopped in those patients with advanced diabetes.

[Slide]

Our safety summary is that a few adverse events were probably related to either study medications rated by the investigators, and that probably related insomnia

occurred only with ofloxacin. There were fewer patients with adverse events, particularly insomnia, for the pexiganan group, and severity and seriousness of cellulitis was greater in the pexiganan patients; the severity and seriousness of osteomyelitis and ulcer infection was greater in the ofloxacin patients.

[Slide]

In conclusion, consideration of use in patients with infection of diabetic foot ulcers should include careful monitoring of the progress of therapy for any medication. Patients sometimes do not improve and need to be carefully followed.

[Slide]

For pexiganan therapy we need to have appropriate patient selection for this local therapy, and avoid therapy locally for patients who have systemic infection, osteomyelitis, exposed tendon or bone or extensive cellulitis. The clinical management should also include debridement, local wound care and minimizing pressure at the ulcer site.

[Slide]

We believe that pexiganan provides a number of potential benefits as a novel topical antimicrobial therapy. It would be the first topical medication studied in this rigorous fashion for the infected diabetic foot ulcers in

outpatients.

It provides an alternative to the physician of local therapy for local infection. It provides an alternative to the healthcare provider when systemic antimicrobials may be of concern, when there are delivery issues for the systemic direct side effects which may be associated; the potential for drug-drug interactions; and, finally, there may be concern about the effects of using, for local infection, a systemic agent which may cause alterations in the individual patient; and, as a public health concern, the microbial ecology.

Finally, as Dr. Lipsky pointed out, it will help focus the patient through their twice a day application of pexiganan cream on the examination and care of their neuropathic foot where it is necessary to visually examine the foot to monitor the progress of therapy.

[Slide]

This new class of antimicrobial agents, of which pexiganan is a member, I believe has a novel mechanism of action. There is no in vitro evidence of cross-resistance to other classes reflective of this novel mechanism, and there is not transferable resistance for the class of magainins or other cationic peptides.

[Slide]

As my last slide, I believe the data I have shown

you leads us to the conclusion that pexiganan acetate cream is safe and effective for the topical treatment of infected diabetic foot ulcers. Thank you.

DR. CRAIG: Thank you. We probably can take five minutes if somebody has a burning question from the committee that they want to ask now, but we will have time later for questions too. Anyone that has a question right now? It looks like everybody needs a break. Let's take our break and we will meet in 15 minutes, which by my clock means 11:20.

[Brief recess]

DR. CRAIG: We will now hear the FDA clinical and statistical presentations.

FDA Clinical and Statistical Presentation

MR. BOSTWICK: Thank you, Dr. Craig, committee members and guests.

[Slide]

My name is David Bostwick. I am a clinical reviewer in the Division of Anti-Infective Drug Products. Dr. Li Ming Dong and I will discuss NDA 20-930 pexiganan acetate cream. Actually, we are going to break our presentation in the middle. I am going to present data up through the efficacy data and then Dr. Dong will make a presentation and I will come back and complete safety and have some brief comments.

[Slide]

I would like to credit the review team for this project, especially Miss Maureen Dillon-Parker, the project manager; Dr. Roberts, the team leader for this project; Dr. Li Ming Dong, who is a mathematical statistician; and Dr. Lin, who is the statistical team leader.

[Slide]

Here is the rest of the team. I would also like to credit Dr. Alex Rokawski for these slides.

[Slide]

A little background -- some of the material I am going to give you will be redundant to what Dr. Holroyd said but I don't think we will waste too much of your time with it.

The NDA was originally submitted July 24, 1998. The proposed indication, and we are abstracting a piece of it here -- topical treatment of patients with infected diabetic foot ulcers caused by susceptible strains of the microorganisms listed below, followed by a list of microorganisms.

[Slide]

As you have already heard, pexiganan acetate is a synthetic 22-amino acid peptide, related to naturally occurring antimicrobial peptides. And, as you have already seen, it has a broad in vitro spectrum of activity.

[Slide]

Some background comments -- as was also earlier alluded to, this indication has not been studied frequently as a specific indication for infected diabetic foot ulcers. There is not a lot of background to go on. At the time of the study design there was no approved drug for the proposed indication. We had extensive discussions both internally and with the sponsor, and ofloxacin was chosen as an acceptable positive comparator.

[Slide]

A little bit about the clinical efficacy studies, which I think you already know about but I will run through this anyway -- there were two separate pivotal studies. Both of them were pexiganan acetate cream one percent, twice daily, with ofloxacin tablets 200 mg. Well, they took 2 200 mg tablets so it was really 400 mg twice daily.

The studies were a double-dummy, double-blind design and multicenter. I think Dr. Holroyd has explained the double-dummy concept adequately. Treatment lasted 14-28 days at the discretion of the investigator. It was to have lasted 14 days. If the patient was showing progress it could go up to 28 days. In any event, after end of therapy there was to be a follow-up visit 2 weeks later.

[Slide]

There were 493 patients randomized to study 303.

As was earlier mentioned, there was also a two percent formulation utilized in the original study design. There was a planned interim analysis to see how the two percent and the one percent were doing against one another. There was no significant difference noted between the one percent and two percent formulations so the two percent formulation was dropped, and no statistical adjustment was made for this procedure. I should mention that the 493 patients here are only one percent pexiganan and ofloxacin patients. In study 304 there were 342 patients randomized. It was only one percent pexiganan versus ofloxacin.

[Slide]

A little bit about the inclusion criteria -- the patients were to have active diabetes. They were not required to be insulin dependent. They were to have a full or partial thickness foot ulcer at least 0.5 cm^2 in area. They must have been able to be treated on an outpatient basis, which means for our purposes that the patients applied their own medications after instruction by the investigator and, as you have seen, the study targeted patients with localized infection who had no systemic signs of infection at study entrance.

[Slide]

This is a very minimal abstract of the inclusion criteria. Infection was defined as presence of purulent

drainage or at least two of the following symptoms: erythema, local edema, induration, local warmth or pain, and/or tenderness to palpation. Osteomyelitis was to have been ruled out in patients on study entrance.

[Slide]

Now we will go to the efficacy parameters. The primary efficacy parameter was clinical response at follow-up. The investigator evaluated each wound at follow-up as cured, improved or failed, and we will give you the definitions for cured and improved in a moment. The cured and improved categories were added together to form a response category.

[Slide]

As a definition for cure, no further signs or symptoms of infection and no need for antimicrobial therapy. The improved therapy was defined as clinical findings significantly improved but incompletely resolved.

[Slide]

We also had a number of secondary efficacy parameters: microbiological response which we will discuss specifically in a moment; combined clinical and microbiological response; wound size and depth; a wound infection score, which includes drainage, induration, pain and other symptoms and was a means of attempting to assess the infection of the wound, and it is different from the

microbiological response; and, finally, a total wound score, which included wound symptomatology, pulses, and wound measurements.

Dr. Li Ming Don will give you a much better summary of the total wound score parameter. I will say that when we analyzed the data we separately analyzed the wound symptomatology and the wound measurements, which are the same thing as the wound size and depth.

[Slide]

Once again, we are going to give you a very abbreviated version of demographics. There is a lot of stuff we are not showing you that we don't think is remarkable. In terms of male versus female, as was earlier mentioned, there was a predominance of males in the studies. I am guessing the reason is because so many veterans hospitals were included in the study centers. We feel that ethnicity and age -- the mean age of the patients was about 58 years -- were balanced.

[Slide]

This has something to do with the treatment history. When we say osteomyelitis and related surgery we mean prior osteomyelitis -- they were not to have had it at study entrance, and prior related surgery. As you can see, the pexiganan group had more prior osteomyelitis. They had more prior related surgeries including amputations than did

the ofloxacin group.

[Slide]

This is just a little bit about treatment history and insulin use. There was slightly more insulin use in the pexiganan group. There were slightly more oral agents used in the ofloxacin group. And we include the mean hemoglobin A1c, just to give you some idea of the kind of control the diabetes of the average patient was under at the time of study entry.

[Slide]

Here is a little something about the baseline wound characteristics. We are giving you here mean wound area and median wound area. We are going to use mean in our presentation. Once again, Dr. Li Ming Dong will give you a presentation of both in her slides. It will give you some idea of what the relationship might be.

For wound depth, I can say for both of these characteristics that the pexiganan wounds were slightly larger, and they were slightly deeper upon study entrance than were the ofloxacin wounds.

[Slide]

This is the primary efficacy parameter. This is the clinical response of patients at follow-up. I should mention that for the per-protocol group, the FDA reviewers altered the per-protocol population as seen from the

Magainin Pharmaceuticals. We put a few patients in; we took a few patients out mainly because of our judgment that the visit windows were perhaps a little too strictly adhered to by Magainin. It resulted in a net gain in the per-protocol patient population of about 40 patients. In any event, this presentation suggests -- and, I am going to read this because it is hard for me to remember -- that it did not meet the primary objective, which was to rule out the possibility that the test products differed more than 15 percent in their effect. Especially in the per-protocol group, the confidence interval does not cross zero.

[Slide]

We thought you might be interested, since the previous slide showed the cures and improves together, in seeing what difference there was in the cures and improves separately. This presentation shows rather effectively that the principal difference in the treatment groups was in the number of cures. The improved patients were comparable between the two groups.

[Slide]

We are now going to go on to microbiological response. This was classified as infection resolved, improving, failure, colonization, superinfection, relapse, reinfection, or inevaluable. We are going to give you the definitions for infection resolved and improving in a

moment.

Since there were very few infection improving patients in the patient group at follow-up we decided to present the results as infection resolved only. We also analyzed the individual pathogen results.

[Slide]

Infection resolved: all initial pathogens are eradicated or culture specimen could not be obtained due to lack of clinical signs and symptoms of infection. We note that this is a relatively high bar to cross -- all pathogens eradicated. Infection improving is at least one but not all original pathogens are eradicated.

[Slide]

I should note that the ITT micro and the per-protocol micro groups simply mean that these groups had a pathogen at baseline. That is how we differentiate them. You can see from this evaluation that the groups are comparable in their ability to achieve microbiological infection resolved, between 40 percent and 46 percent, depending upon what group and what evaluation one used.

[Slide]

This is the combined response at follow-up. This simply means these are patients with clinical responses of cured and a microbiologic response of infection resolved. This is what Dr. Roberts likes to call that the data talk to

each other. The clinical evaluation and microbiologic evaluation were conducted separately, with separate scales, as you can see. These are the patients who were both cured clinically and cured microbiologically. As you can see, the numbers are relatively low, but this is a very strict criterion for efficacy so we are not surprised to see numbers this low. Once again, they are comparable between the groups and we should mention that it is driven much more by microbiological response than by clinical response because you are limited by the number of patients who had pathogens.

[Slide]

Here is our pathogen response. A little bit of background here, these pathogens in the denominator are numbers of pathogens that were seen in this group at baseline. The numbers in the numerator are the numbers that were eradicated at follow-up. In this evaluation relapses were counted as failures. What you can see from this data is that for S. aureus and group B strep. ofloxacin was somewhat more successful in eradicating these pathogens at follow-up. For E. faecalis the numbers were comparable.

[Slide]

We haven't gone through the exercise of making graphs for all these. We will say that the following wound parameters we found similar between the two groups, which is

to say reduction in wound symptomatology such as erythema, edema and purulence; reduction in the wound infection score; reduction in the wound depth; and reduction in the total wound score. Once again, Dr. Li Ming Dong will give you a much more extensive evaluation of the total wound score when she makes her presentation.

[Slide]

We are going to give you a look at the mean wound size reduction for this study, although there doesn't appear to be any difference between the groups, simply because Dr. Dong will discuss this later. As you can see, the ofloxacin wounds got smaller, somewhat smaller but there was no significant p value between the two reductions.

[Slide]

Now I am going to move on to study 304. Once again, we are sort of doing bare bones demographics here, but again males were the preponderant number in this study, and ethnicity and age -- the mean age in this study was 60 years, were balanced.

[Slide]

A little bit about treatment history. For osteomyelitis there was a relatively even balance. The prior osteomyelitis in the treatment cohorts was about the same. Once again, for related surgeries and amputations, there were more related surgeries and amputations in the pexiganan

group in study 304 than in the ofloxacin group.

[Slide]

Treatment history -- this is not a lot different than what you saw in study 303. We only present it to give you some idea of what insulin use was and how the diabetes was being controlled. We don't find anything remarkable in these figures.

[Slide]

Here are some baseline wound characteristics. Once again, we are presenting mean and median. The ofloxacin wounds were slightly larger. They were also slightly deeper. The median values were not different for wound depth for ofloxacin and pexiganan.

[Slide]

This, once again, is the primary efficacy parameter. In this study the primary objective, which was to rule out a 15 percent difference between the groups, has been achieved in clinical response at follow-up. The groups are quite comparable and the confidence intervals are satisfactory.

[Slide]

Once again we have broken out cures versus improved's. So, you can see there really isn't much difference between the groups. They are comparable both in numbers of cures and numbers of improved patients, and we

don't see anything remarkable about this, except to say that here it is.

[Slide]

There is a difference here. These are microbiological infections resolved at follow-up. You may remember that we have infections resolved, infections improved, and so forth. The ofloxacin group apparently did better in resolving microbiological infections at follow-up. The pexiganan cohort is on the lower end of the point estimate here. Although these are relatively small numbers of cures and relatively small numbers of patients, we should state that.

[Slide]

Once again we have the combined response. This is simply all those patients who were cured clinically and all those who were cured microbiologically. Once again, because it is driven by the microbiological response the point estimates come out on the low side for pexiganan.

[Slide]

These are the pathogen results for study 304. All three are the most frequently seen pathogens, and these are the same three pathogens you saw in study 303. In our estimation ofloxacin was about 20 percent better in eradicating those pathogens than pexiganan was. Once again, I would note that the denominator is the number of pathogens

seen at baseline and the numerator is the number of pathogens eradicated at follow-up.

[Slide]

We will once again say, without going through the graphical presentation, that by the following secondary means of evaluating the study we did not find significant differences between wound symptomatology, reduction in wound infection score; reduction in wound depth; and, reduction in total wound score.

[Slide]

As far as mean wound size goes, there does appear to have been a difference. Ofloxacin in this study had been better in reducing the wound size, 149 mm^2 to 90 mm^2, which has a p value of 0.08, and in per-protocol the difference was 132 mm^2 versus 79 mm^2, which has a p value of 0.035.

Dr. Dong is now going to give her presentation and then I will come back and finish up with some safety information and some final comments.

[Slide]

DR. DONG: I am Li Ming Dong, the statistical reviewer for this NDA. Mr. Bostwick has just presented the efficacy results with respect to clinical and microbiological results. This presentation will focus on wound measurements in these two studies.

[Slide]

Here is an overview of my talk. First, I will discuss mean score, its components; its changes over time; and the comparison between the two groups. Next, I will discuss the wound measurements with respect to wound size and wound depths. All the results will be presented based on the ITT population, which is all randomized patients, and the per-protocol population, which is the protocol-defined evaluability criteria.

[Slide]

Here is a list of 14 parameters that the total wound score was counted from. The total wound score was the summation of all scores for each parameter. The mathematical range of total wound score is from 3-80. High total wound score indicates a severe wound. Since the total wound score is a composite score, it is important that each component score changes in the same direction as the total wound score does.

[Slide]

In this plot the average total wound score is plotted on its actual value, while the mean values of each component are plotted on top of the other to give us some idea about how much its components contribute towards the total wound score. It shows that all components of the total wound score decreased with time, as the total wound score did. It also shows that the scores for wound symptomatology

contributed much more than wound granulation, wound size and wound depth score.

[Slide]

This slide is a similar plot for study 303 ofloxacin group. The general trend is similar to what has been observed in the previous graph. Graphs for study 304 also show a similar pattern but they are not presented here.

[Slide]

The comparison of the pexiganan and ofloxacin groups in total wound score is shown in this graph. Lines of same color indicate the same study. The solid lines are for pexiganan the group and the broken lines are for the ofloxacin group. Both studies show that the total wound score increased with time. The two treatment groups were compared with each other in total wound score reduction at every follow-up. No statistical significant difference was found. The two treatment groups were also compared with respect to changes in component scores. No significant differences were observed, in fact, in wound size scores in study 304 in the ITT population.

[Slide]

Next, I will focus my discussion on wound size and wound depth.

[Slide]

There are a few reasons why we are particularly

interested in wound size and wound depth. First, wound size and wound depth are both objective endpoints as opposed to a clinical outcome endpoint. Second, both are clinically relevant, and both were predefined in the protocol. Third, the sponsor plans to make claims with regard to these two measurements.

[Slide]

This slide shows the number of missing values for wound size at the follow-up visit. We can see from here that in study 303 11 and 10 patients were missing at the follow-up visit. For study 304, 20 and 10 patients in each arm were missing out of 171 patients. For the per-protocol population they are also about evenly distributed between the two treatment groups.

[Slide]

This slide shows median wound size by study visits for study 303. The solid red line stands for the pexiganan group; the blue broken line represents the ofloxacin group. Both pexiganan and ofloxacin groups demonstrated wound size reduction over time. Wound size of both treatment groups started with 125 mm^2 and by the follow-up visits both were below 50 mm^2.

[Slide]

For study 304, this shows again that wound size decreased over time. Notice that here there is a cross here.

Whether this indicates a difference between the two treatment groups in wound size reduction will be discussed in just a few minutes.

[Slide]

This graph plots wound depth at each study visit for study 303, similar to wound size. The average wound depth also decreased over time. This is not unexpected since wound size and wound depths are correlated with each other. Values of average wound depths of the two groups were quite close at each study visit.

[Slide]

This is the same graph for study 304 for wound depth. It also shows that the values of the wound depth are quite close at each study visit for the two treatment groups.

[Slide]

Since wound size reduction measures wound healing, here is a graph which shows the distribution of changes in wound size at follow-up. The blue bars are for the pexiganan group, and the transparent bars are for the ofloxacin patients. The horizontal scale for each bar is 50 mm^2. We observed a wide range of changes in wound size for both treatment groups. Most of the values fell below zero, which means that most of the patients had wound size reduced, but not all of them.

[Slide]

This graph is a similar plot to the previous one for study 304. Again, the blue bars represent the test drug and the bars with the lines represent the control drug. The pattern is similar to study 303 in that for both treatment arms most of the patients have reduced wound size. In a few patients wound size increased. All stayed the same at the follow-up visits. Distribution of the ofloxacin group seems to have a slight shift to the left.

[Slide]

For this slide, first let me explain how the numbers were obtained. Since how much wound size decreases at follow-up visits measures wound healing, wound reduction for each patient was calculated by subtracting wound size at follow-up from the baseline wound size. Therefore, each patient has a measurement of one reduction. We want to compare the two treatment groups with respect to this wound size reduction. Naturally, we compared the mean reduction or median reduction of the test drug and the control group.

This table displays some key values for the comparison. For example, minus 23 here is obtained using the average wound size reduction in the test group, minus the average wound size reduction in the control group. So, this implies that the ofloxacin group has a larger wound size reduction. It means that among all randomized patients, on

average ofloxacin patients had about 103 mm^2 more reduction in wound size than the pexiganan-treated patients. If we look at the per-protocol patients, the ofloxacin group had 36 mm^2 more reduction than the pexiganan group.

The median reduction for the two groups is very close. None of the p values associated with the differences reached the statistically significant level. However, observing a non-significant p value does not imply that the two treatment groups are equivalent in wound size reduction. This study may just lack the power to detect the difference between the two treatment groups.

[Slide]

This table is a similar table to the previous one but for 304. In this study, ofloxacin-treated patients showed a larger wound size reduction, no matter which population, no matter whether measured by mean or median. The average reduction for ofloxacin is 59 mm^2, more than that of pexiganan-treated patients, with a p value of 0.008 in the ITT population.

Comparison in median size reduction also indicates wound size in the ofloxacin group was reduced more. The p values obtained from Wilcoxon Rank-Sum test is significant for the ITT population but not for the per-protocol population.

[Slide]

An explanatory analysis was performed to see if the baseline wound size can explain the differences between the two treatment arms in wound size reduction. The adjusted differences between the two treatment arms are presented in the lower part of this table. They are obtained from linear regression using wound size reduction as the response variable, treatment allocation and the baseline wound size as the explanatory variable.

This table shows that even after adjusting for baseline wound size the ofloxacin group still had a larger reduction in wound size. For study 303 ITT population on average the wound size in the ofloxacin arm was reduced 27 mm^2 more than that of the pexiganan patients with the same baseline wound size. That is, if the two treatment arms started with the same wound size at baseline, at follow-up the wound size of the ofloxacin group would be 27 mm^2 smaller than that of the pexiganan group.

Other values can be interpreted the same way. For the per-protocol population in the same study the adjusted difference between the two treatments is 53 mm^2, with a p value of 0.009. Results of study 304 remained similar with or without baseline adjustments, no matter which population we are looking at. All p values for study 304 suggested that the differences between the treatment groups in wound size reduction were statistically significant favoring ofloxacin.

[Slide]

We go one step further to examine two extreme cases, patients completely cured and patients with wound size increased or not changed at the follow-up visits. This table displays the percentage of patients with healed wounds in the ITT population. Healed wounds are defined as wound size reduced to zero at the follow-up visit. Patients with missing wound size at the follow-up visit were treated as not healed. Although the p value did not reach the statistically significant level, both studies show that fewer patients in the pexiganan group healed completely than in the ofloxacin group. If patients with missing wound sizes were dropped the results remained qualitatively similar.

[Slide]

This table displays the percentage of patients with no wound reduction or increased wound size at the follow-up visit. Patients with missing values were considered as wound size reduced. Again, the results were in favor of the ofloxacin group in both studies. The percentage of pexiganan-treated patients with wound size increased or not changed was 8 percent higher than that of the ofloxacin-treated patients in both studies.

In study 303 this difference is statistically significant, with a p value of 0.024. In study 304 the difference is marginally significant. If patients with

missing values were dropped the results also remained qualitatively similar.

[Slide]

Although a lack of statistical significance is not a demonstration of equivalence, we found the following: No significant differences between the two drug groups were observed in reduction in total wound score and its component score, except in the wound size score.

In study 304, the ofloxacin patients had a statistically significantly larger reduction in wound size over the pexiganan group. In study 303, the difference in wound size reduction is statistically significant only after adjustment for baseline wound size.

I will give it back to Mr. Bostwick to continue his presentation.

MR. BOSTWICK: There are a few more slides.

[Slide]

I am briefly going to go over the safety. We have obviously not listed all the adverse events seen, but simply the most frequent or the most remarkable. You can see that 42 percent of the pexiganan patients versus 46 percent of the ofloxacin patients reported at least one adverse event. The numbers are reasonable comparable. There are a few more cellulitis patients in the pexiganan group. Obviously for insomnia there was a greater predominance of patients in the

ofloxacin group who had insomnia at some point during the trial.

[Slide]

These are withdrawals. We, once again, haven't listed all the withdrawals. You can see that 11 percent of the pexiganan patients withdrew in connection with some adverse event; 9 percent of the ofloxacin patients also withdrew in connection with some adverse event. There were more cellulitis sufferers, for lack of a better term, in the pexiganan group. The other numbers are relatively comparable, with exception of vesicular rash in the pexiganan group.

[Slide]

Serious adverse events -- once again, we have not listed them all, but 12 percent of pexiganan patients had at least one serious adverse event; 9 percent in the ofloxacin group had at least one serious adverse event. It is seen that the cellulitis numbers are larger for pexiganan and osteomyelitis numbers are larger for ofloxacin. I think that is all I have to say about that slide.

[Slide]

Briefly, there were four predictive skin sensitization and/or irritation studies performed with pexiganan acetate one percent and two percent creams. All four of these studies indicate that pexiganan acetate has a

potential to cause mild sensitization in patients. However, we did not see in the clinical studies adverse events specifically reported as far as sensitization. So, we simply bring this to your attention.

[Slide]

General considerations -- we believe the purpose of the antimicrobial in the setting of an infected diabetic ulcer is to reduce the pathogen burden and to resolve the infection so that wound healing and closure can occur.

[Slide]

Just in general in the scope of the trials, the original requirement was for two adequate and well-controlled trials which, hopefully, would corroborate each other. It was agreed that ofloxacin was suitable as the active control but we recognize that ofloxacin was a relatively stringent comparator for a topical product. The studies were designed to demonstrate equivalence of pexiganan cream one percent to ofloxacin with a clinical outcome at follow-up in the per-protocol population.

[Slide]

These are our final two slides. As you consider the questions, here are items we think you might like to ponder. To date, acquired resistance has not been reported with pexiganan acetate. In one of the two pivotal studies, pexiganan acetate did not meet the defined objective of

ruling out a 15 percent difference between the test articles.

[Slide]

In both studies the wound size of the patients treated with pexiganan acetate was reduced less than the wound size of the patients treated with ofloxacin. In both studies, eradication rates for S. aureus and group B strep. appeared to be higher for ofloxacin. Finally, dermal sensitization tests indicate that pexiganan acetate is a mild sensitizer, though we did not see this in the clinical studies.

I think that finishes my presentation. I would also like to thank John Mahoney, our excellent audiovisual person. Dr. Craig, do you want to do questions now or do you want to wait?

DR. CRAIG: Yes, we can do some questions because setting up the machines is a problem. So, people who have specific questions about the FDA's presentation, we can do that now. We will save five minutes at the end for our public hearing. All we have is one letter to read. So, we have about 25 minutes now before the scheduled lunch time for questions. Questions from members? Yes, Dr. Murray?

DR. MURRAY: Somewhere in reading the information coming into the meeting, in a couple of places there was an FDA statement about a 50 percent reduction, as I recall, in

wound size, or 50 percent clinical response would be considered appropriate in this --

MR. BOSTWICK: I think we got that number from the guidance for skin and skin structure studies. Well, that number is really 50 percent for microbiology patients. Where we got the 50 percent was we looked at some references that the Magainin people were kind enough to send to us, and we also looked at the ofloxacin results. Now, those are probably more seriously ill patients, but we found about a 50 percent cure rate amongst the Trovan patients. So, we took that to be an acceptable number, although we don't have a real basis for it outside our sense of it.

DR. CRAIG: Dr. Norden?

DR. NORDEN: One of my concerns deals with the microbiologic response, and I am interested to know sort of what percentage -- the patients who have a failure clinically are called a failed microbiologic response whether or not you can get cultures as opposed to patients who were failures but from whom you isolated Staph. aureus at follow-up or group B Strep. Because, you know, there is a clear difference and it doesn't look particularly good for pexiganan. So, I guess I am curious to know how much of this is just a reflection of the clinical data as opposed to actual microbiologic failure.

DR. CRAIG: I would add also, from the other side,

if there was no culture done they were called eradicated. So, I think what we are trying to find out is what was the degree of elimination in those things where we truly have a culture at the beginning and a culture at the end.

MR. BOSTWICK: Well, the data we gave you are the data we have. We don't have a reason to deny that if you have a clinically cured patient you can evaluate that patient as also being microbiologically cured. The clinical evaluations and the microbiological evaluations, in terms of infection improvement and infections resolved, were done separately. I don't know that we have any backup on that. We do have some backup on what happened to patients who had various pathogens and failed.

DR. CRAIG: But I guess the question that Carl is asking is, let's say that Staph. aureus was one of your initial three organisms --

MR. BOSTWICK: Right.

DR. CRAIG: -- and the wound failed --

MR. BOSTWICK: Right.

DR. CRAIG: -- culture was done and no Staph. aureus was grown, would that still be called a failure for Staph. aureus because it was one of the original pathogens and it failed therapy?

MR. BOSTWICK: It should have been.

DR. CRAIG: Even though it might not have been

recovered on a subsequent culture?

MR. BOSTWICK: Right. I think that is right. Someone from Magainin might want to contradict me about that.

DR. HOLROYD: Dr. Craig, I will try to understand your question, the question was --

DR. CRAIG: The question is if a wound failed and Staph. aureus was one of the organisms that was recovered initially and, let's say, a culture was done at the end with failure but the Staph. aureus wasn't recovered anymore, would that still be called a failure for Staph. aureus because it was one of the original pathogens?

DR. HOLROYD: The per-subject microbiological response, if there was a Staph. aureus at the beginning and not one at the end among a clinical treatment failure -- I believe is the question and I think, as Mr. Bostwick has tried to outline, there are really separate evaluations. So, really the responses that would be possible are varied. If all the organisms were gone it could still be microbiologically infection resolved despite a treatment failure. That happened very rarely, as I can best recall. If the Staph. aureus was still there but other pathogens at the baseline visit were not and nothing new had grown out, that would be called infection improved on a per-subject basis. If there were new organisms which had grown out during the

course of the study and the patient was a treatment failure, that would be called superinfection.

DR. CRAIG: Dr. Gerding?

DR. GERDING: Can someone explain how cellulitis was determined as a safety factor, and how it was differentiated from possible sensitization that might have occurred?

MR. BOSTWICK: We simply took the judgment of the investigator. If he said it was cellulitis, we didn't have a way to go back and check him so we took his word for it. I admit that is a possible confusion.

DR. CRAIG: Yes, Dr. Roberts?

DR. ROBERTS: I would comment though that certainly for the withdrawals for cellulitis as serious AEs, if you look, most of those patients went on to receive systemic, either oral or parenteral therapy when they were called as having cellulitis as an adverse event.

DR. CRAIG: I guess I would ask did you do any, for example, logistics regression to see if possible previous osteomyelitis or history of osteomyelitis, or a history of amputation had any impact on the probability of developing a good outcome?

MR. BOSTWICK: We did not. I think the Magainin folks did and, once again, they can contradict me. I don't believe that they were able to establish any direct

connection. I think there is a suggestion -- is that right?

DR. HOLROYD: I think as Mr. Bostwick is referring to, obviously there are a lot of variables going on in these patients. I could show you, if the committee is interested, data where we look at patients, whether they had the history, for example, amputation or foot surgery, the history of osteomyelitis, and show you how the clinical response varied whether they had the history or not.

I can tell you that in general in the 303 study a large component in the difference in clinical outcome occurred in the patients that had a difference in history of amputation. There is also some effect there for history of osteomyelitis broken down in a simplistic way.

In the 304 study, interestingly, pexiganan had very similar point estimates of the clinical response for people with or without this history, and ofloxacin had slightly lower point estimates of the response for people with the history of amputation or osteomyelitis in that study.

I would be happy to show you the data. I don't know if you would like to see that slide now.

DR. CRAIG: I would like to see it sometime --

DR. HOLROYD: Yes, sir.

DR. CRAIG: -- but is it set up?

DR. HOLROYD: I am told it would have to be set up

after lunch, Dr. Craig.

DR. CRAIG: Fine. The other thing that I am also interested in is whether anyone has done logistics also to look at wound size to see if that had any impact on whether there was a favorable outcome. I guess the question I would ask the statistician also is were the larger ulcers -- you said you made an adjustment. Can you get out of the database that large ulcers healed to the same degree as smaller ulcers, or is there a percentage, or what kind of an adjustment did you actually do? Could it be that when you have larger ulcers they are not going to heal as much as what you have when you have a smaller ulcer?

DR. DONG: I agree with what you are saying. Even though we didn't do it, I believe the larger ones will be harder to heal but we didn't do that analysis. The one we did, basically we tried to see the kind of effect of the baseline in terms of wound side reduction.

DR. CRAIG: Dr. Gerding?

DR. GERDING: A similar question, in analyzing the differences in reduction in wound size, did you include all ulcers, including those that were failing which might have actually enlarged in size, or did you do a subanalysis that confined your size reduction only to those patients who were actually showing a response?

DR. DONG: We included all the patients.

DR. GERDING: So, you have the ones that actually grew as well as the ones that were getting smaller?

DR. DONG: Right.

DR. CRAIG: Dr. Parsonnet?

DR. PARSONNET: I have a question about the wound size reduction. I guess in your multivariate analysis you looked at means -- you reported the mean, and in one of them you reported the median, in one of the two studies. But when you looked at the means and medians they were pretty different in, I guess, 303. I am wondering whether looking at the mean is really appropriate for that study because there was a fairly big skew in the change and whether a median would have been more appropriate to look at in that particular analysis.

DR. DONG: Yes, I believe the distribution is a little skewed. That is what you can see from the histograms, especially for study 304 where there are a few patients with a larger reduction. But what I feel in this case is that both the means and the medians are interesting variables to look at. One reason for the average is that those reductions, those are actual clinical measurements. I mean they are clinically observed. So, I don't feel it is appropriate to drop those patients who are on the lower end, I mean to exclude them from the study.

DR. PARSONNET: Right, but when you looked at the

multivariable using the medians in that one study, was there a significant difference there?

DR. DONG: No, in a multivariate analysis basically we look at the mean rather than the median.

MR. BOSTWICK: What she is asking is was there a difference if you did medians.

DR. PARSONNET: Yes, if you did medians.

DR. DONG: We didn't do medians.

DR. CRAIG: Yes, Dr. Miller?

DR. MILLER: What were the data that supported the slight sensitization qualities or properties of the preparation?

MR. BOSTWICK: They did four separate studies. They had a number of different test preparations, but in each of the studies the investigator evaluated the results as being that. In a classic patch sensitization study pexiganan has the potential to be a mild sensitizer, and that was simply because they showed more sensitization on challenge than the other ingredients that were included in the study, say, the vehicle or saline, or something like that. There are standard protocols for those, and I was actually going to try and make a slide up to explain it but it is truly Greek to try to understand the way those things are performed.

There is an explanation of them in the FDA review

in your package, and it will tell you exactly what products were tested, and we agree with the investigators' evaluations of them. But those are not clinical studies; those are purely lab studies in which healthy people are patched with the drug; covered up, left for a few days and then you grade the irritation.

DR. CRAIG: Dr. Parsonnet?

DR. PARSONNET: I was wondering whether either the sponsor or the FDA has any sense of what proportion of patients who had any diabetic foot ulcer were considered to be infected. This was a lot of the foot ulcers that came in, because we heard in the initial presentation that most foot ulcers don't need antibiotics at all. So, the question I have is were people really being pretty rigorous about trying to take real infections or were they really taking a lot of people who may not really have been necessarily --

MR. BOSTWICK: Well, after working so hard on the protocol we looked back and thought, after having had experience with other things, that we left a hole in it -- we didn't ask for WBCs as an entrance criterion. In any event, we looked at the data and we asked Magainin to go back for the wound infection score which was to measure things we thought were connected to infection, to take out those who had a lower wound infection score and simply calculate numbers of those who had a higher wound infection

score. They were slightly different but not terribly different. In terms of patients who were actually infected, I don't know, I think we only left out something like 13 or 14 percent of the patients with low wound infection scores. If you can accept that symptomatology, the erythema and things like that, and purulence obviously, as signs of infection, then I think we probably had about 85 percent of the patients in the study we were pretty sure were infected.

DR. CRAIG: Dr. Murray?

DR. MURRAY: I think what Dr. Parsonnet was alluding to is out of what proportion that were initially screened were then actually eligible for the study on their basis, not how many FDA excluded over those that the company had included.

MR. BOSTWICK: I don't know the answer to that. Do you have any idea?

DR. HOLROYD: The number screened? I would have to look for that information. I don't know that information now.

DR. CRAIG: Maybe after lunch?

DR. HOLROYD: I will have to see if that information was captured, Dr. Craig. It is not something I have discussed previously.

DR. CRAIG: Dr. Miller, did you have another question?

DR. MILLER: For those patients who during the study developed osteomyelitis, how was the osteomyelitis diagnosed?

MR. BOSTWICK: I don't know the answer to that. Do you know the answer?

DR. HOLROYD: The question is the osteomyelitis diagnosis in the study. We took, as Mr. Bostwick outlined for cellulitis, the investigator's reported diagnosis of osteomyelitis and, obviously, that could be done by the usual means for these patients. I know it is a complex issue in these patients to establish that diagnosis but in terms of the incidence of osteomyelitis for the two treatments, essentially what we did, similar to cellulitis, was to take the investigator's diagnosis for that patient, and it was often concomitant for serious or severe either osteomyelitis or cellulitis if the patients were in the hospital with that treatment. So, that was a correlative decision of the investigator as well perhaps.

DR. CRAIG: Dr. Gerding?

DR. GERDING: I am curious about what the prospects are for magainins ever being used for systemic therapy, and whether that is likely given the sort of marginal track record of membrane active drugs as systemic agents. I would be interested in any comment.

MR. BOSTWICK: I don't have any comment on that.

DR. HOLROYD: Dr. Gerding, it is certainly something that is of potential interest to us. The delivery of high amounts of magainins to the systemic circulation to achieve a sufficient MIC value to treat systemic infection remains with some technical challenges, and we are certainly interested in looking at this further, and potential modifications of the baseline peptides and how this may impact potentially in this area.

But just to fill that out further, we do not currently have any clinical studies even of an early nature going on with systemic magainins at the current time.

DR. CRAIG: Yes, Dr. Rodvold?

DR. RODVOLD: The question I have is in the proposed indication or labeling, Dr. Lipsky presented a categorization or classification called mild, moderate and severe, and other FDA labeling for infections has mild, moderate and severe indications and I don't see that language at all in this proposed indication. Is that something being considered or something which we should consider in the discussions today to reflect the population that was studied?

MR. BOSTWICK: Yes, I think we would have to. We haven't really thought about it in terms of writing a label for it at this point but, plainly, we are going to have to describe in some way that is meaningful what types of

patients were studied so that folks who would be using the drug would have some idea of who should or should not be tried on it.

DR. CRAIG: Yes?

DR. O'FALLON: In studying the booklets, I was struck by the fact that there was quite a bit worse fallout or dropout rate in the cream group versus the oral group in some many of the analyses. Since the endpoint is supposed to be the per-protocol group I was wondering why there was more of a dropout, as many as 15 or 20 patients in each of the arms, that were dropped out of the cream.

MR. BOSTWICK: The only thing I have really thought about here is that -- I know that at least in one study, in one category, there was a relatively large difference in patients who dropped out for concomitant medications in pexiganan. My guess is -- I don't know this, that the concomitant medications they were getting were for other diseases that they caught while they were on the study, and the ofloxacin that the other group had on board may have protected them in some way so that they weren't getting the same kinds of other diseases that the group on pexiganan were. That is really a guess.

DR. O'FALLON: What do the people from the company think?

DR. HOLROYD: It is true, and I think we showed

that taking systemic ofloxacin would help treat things such as urinary tract infections or perhaps the development of urinary tract infections, or potentially development of bronchitis or sinusitis, and there were a number of patients in the pexiganan group who were placed on systemic antimicrobial agents for treatment of other infective conditions. If it was not felt to be related, as the investigator told us, to the agent being started because of diabetic foot infection but related to some other condition where in his or her opinion systemic antimicrobial therapy was indicated, then that was taken into account in the data analysis, and that did occur more commonly with pexiganan.

DR. O'FALLON: Yes, but still it is a problem because the bottom line analysis has to be on the per-protocol group, and there were a lot of people that were removed for this reason. What kind of bias could this be introducing into the per-protocol group -- you know, the comparison?

DR. HOLROYD: They wouldn't be included in the per-protocol group unless they were a treatment failure for either therapy. So, if they were not a treatment failure, we weren't sure that they were going to fail, then they were excluded from the per-protocol analysis. If they were a treatment failure at that point, then they were included in the per-protocol analysis. I believe Mr. Bostwick would

concur that that was the way that the treatment failures were carried forward during the study.

DR. CRAIG: I am reading it sort of like 60 versus 50. I mean, it is not a huge difference.

MR. BOSTWICK: No, it is not a huge difference but there is a difference.

DR. CRAIG: Dr. Reller, do you have a question?

DR. RELLER: The proposed indication is for infected diabetic foot ulcers. Could we hear what the current list of agents is that are approved specifically for this purpose?

MR. BOSTWICK: The only one I know is Trovan, trovafloxicin.

DR. RELLER: Secondly, how in this study -- or is it proposed to distinguish between colonized wet wounds with a rim of thick callus in infected diabetic foot ulcers?

MR. BOSTWICK: I think that is a problem. I don't think most people will culture these, and one of the problems we will have in writing the label is figuring out how we are going to identify the patients who should be treated with the drug.

DR. RELLER: And where does one separate an infected diabetic foot ulcer from one with sufficient -- the term was "extensive areas of cellulitis." Where do you draw the line between the extensive cellulitis associated with an

infected foot ulcer in a diabetic patient who would not be a candidate for topical therapy from the patient who would be a candidate, who has infection and is not merely colonized with a mixture of organisms in a soupy wound in a patient with diabetes?

DR. CRAIG: I thought in this study it was 2 cm of erythema.

DR. HOLROYD: I the protocol we called it not "extensive cellulitis." What I was referring to, I believe, was an informal working definition when investigators would ask us about this. But you will note that it is not defined in the protocol. I wouldn't disagree with this working definition. I think this more specific question came from the investigators sometimes during the study, and we have discussed this. I really wasn't aware of this history until recently when we had our investigators together to look at the data from the studies which they collected for us. Perhaps it would be useful, if it is okay, to have Dr. Lipsky make a few comments.

DR. LIPSKY: I think Dr. Reller's question is a very good one and needs to be carefully considered. As Dr. Miller mentioned, you can have patients who have diabetic foot ulcers that have callus and the callus can sometimes be malodorous, and the wound can look "soupy" or at least have liquid material in it.

I think that sometimes that is difficult to distinguish from an infection but in my view most of the time it is quite different from a truly infected foot ulcer. The infected foot ulcer has purulence to it, and I don't think that a callus truly has purulence. That is what we would call pus, or under the microscope would predominantly be white cells and organisms.

I think that the infected wounds that have a small rim of cellulitis would be appropriate candidates for topical therapy. When it gets out beyond, arbitrarily, 2 cm we have felt that that was probably beyond the point where we would want to use a topical agent. Many of the infected foot ulcers don't have any cellulitis, but simply the wound itself has purulent material; it is tender and it is painful; and there are other signs of inflammation. I think most of the time one can make the distinction between an infected and an uninfected ulcer on clinical grounds and -- I will leave it at that.

DR. RELLER: Just to follow-up on this point, there was an attempt or there was a proscription for using swabs. So, there was an attempt to get curettings and aspirates, and we heard a lot about the microbiology. Were any Gram-stain smears done on any of that material, and what did it show? I recognize the limitation for assessing infection with a peripheral white count in these patients,

but what about what the curettings actually showed to compare with the culture? And, is it possible to really interpret the cultures without knowing what the Gram-stain of the curetted material showed?

DR. HOLROYD: Dr. Reller, we have not formally analyzed in any way the Gram-stain and its relationship to the culture results. We do have historically types of studies done for tissue curettage which we used, which Dr. Lipsky could review, if that is of interest. My impression from reviewing patient by patient the culture results, and looking at the Gram stains is that most did have a positive Gram stain that correlated reasonably well -- I just say reasonably well as an impression -- with the culture results. I would be happy to try and flip through some of that in the lunch break and try to give a marginally more informed impression, but I don't have any specific data analysis of the relationship between the Gram stains and the cultures for you.

DR. CRAIG: Dr. Norden?

DR. NORDEN: I want to follow up on Dr. Reller's first question, which Dr. Lipsky answered but I guess I would like to press it a little bit. I think you are an expert in the area of diabetic foot infections and I would feel very comfortable with your evaluation of whether a patient has an infection or a merely colonized wound. But

the limitations that are being proposed -- I was going to bring this up in the question period but I might as well do it now -- the limitations that are being proposed on the claim of no systemic infection, no osteomyelitis, no exposure of tendon or bone, extensive cellulitis I think really call for experienced clinical judgment and are not necessarily simple. And, that is one of my real worries, that if this product is approved it will be used in situations where one should use systemic therapy, or it will be used where no therapy would be needed. And, I would like to hear Dr. Lipsky's response.

DR. LIPSKY: Yes, Dr. Norden, I think you are right that both could happen. If either happen, it would be of concern. What I can tell you is that we did bring in a large number of investigators, I think close to 80 different investigators in the two studies. All of them were seeing or thought they would see patients who had diabetic foot infections. So, by that criterion, it might be more than an average clinician. But, with a one-hour training session, going through some slides and a video, we were able to fairly comfortably say that these investigators could enroll appropriate patients, and in reviewing the data it appears as if they did enroll appropriate patients. There were very few patients who were either uninfected or so severely infected that topical therapy appeared to fail them.

So, I do think that the types of doctors -- podiatrists, physicians and others who are treating these patients can, as demonstrated from our studies with the investigators used, make that distinction reasonably well, although I completely agree that the potential exists for either under- or over-treatment.

DR. CRAIG: Last question before we have a break for lunch, and then we will come back in the afternoon. Dr. Gerding?

DR. GERDING: Ben, I wanted to ask you how patients in this study qualified compared to the patients that you have published in the cephalexin-clindamycin study. Is this a comparable group? I know some of them probably wouldn't have qualified because of cellulitis. How do those patients compare from your published study?

DR. LIPSKY: Yes, they are actually quite similar. For those who may not be aware, we published a study in 1990 comparing oral cephalexin against oral clindamycin, which actually was the first published study of oral outpatient therapy of diabetic foot infections. Prior to that it was felt that most needed to be hospitalized. These patients are quite different, with the single exclusion, as Dr. Gerding points out, that we did enroll patients who didn't have an ulcer but had primary cellulitis in our earlier study, and we would not have enrolled somebody who didn't have an ulcer

in this current pexiganan study.

DR. CRAIG: I am going to ask Kathleen Reedy to read the letter that we received from the American Podiatric Medical Association. It is the only part that we have in our public response period. Then, after this, we will take a our lunch break and then we will meet back at 1:15.

Open Public Hearing

MS. REEDY: This is the only submission for the open public hearing, from American Podiatric Medical Association, and comes from Terence Albright, DPM, president:

The American Podiatric Medical Association is the premier professional organization representing the nation's doctors of podiatric medicine whose members provide the majority of all foot care services in the United States. The APMA would like to provide information to the Food and Drug Administration's Anti-Infective Drugs Advisory Committee, who is reviewing the safety and effectiveness of pexiganan acetate for the treatment of infections in diabetic foot ulcers.

Diabetes is a serious disease afflicting approximately 16 million people or approximately 6 percent of the population in the United States. Each day, approximately 2200 people are diagnosed with diabetes, and this year alone 800,000 people will be newly diagnosed. Many

people first become aware that they have diabetes when they develop one of its life-threatening complications.

Diabetic foot ulcers, as well as other foot problems are a major burden for both the individual and the healthcare system and may increase as the population ages. Fifteen percent of all patients with diabetes will develop foot ulcers during their lifetime, and 20 percent of these ulcerations will lead to amputations. In fact, 86 percent of lower extremity amputations were preceded by diabetic foot ulcers. More than half of all lower limb amputations in the United States occur among people with diabetes. From 1993-1995, about 67,000 amputations were performed each year among people with diabetes. After amputation, the chance of another amputation of the same extremity or of the opposite extremity within 5 years is as high as 50 percent. The 5-year mortality rate after lower extremity amputation ranges from 39 to 69 percent.

Foot disease is the most common complication of diabetes leading to hospitalization. In 1995, foot disease accounted for 6 percent of hospital discharges listing diabetes and lower extremity ulcers, with an average hospital stay of 14.7 days. The total annual cost associated with diabetes foot disease is estimated to be more than a billion dollars.

The American Podiatric Medical Association

believes that new therapies to treat infections in diabetic foot ulcers are necessary to improve the lives of people with diabetes and to try to decrease the incidence of lower extremity amputations.

We understand that pexiganan acetate one percent topical cream assists in the treatment of infections in diabetic foot ulcers. If this topical treatment is shown to be safe and effective, APMA feels that it will contribute to the ongoing efforts to reduce the high personal and economic cost associated with diabetic foot disease.

The American Podiatric Medical Association appreciates the efforts of the research community and the FDA to provide safe and effective treatment modalities for diabetes foot disease and its complication. Terence Albright.

DR. CRAIG: Before we break, I just want to find out if there is any information that people would like the sponsor to collect or try and have so that they can be very efficient in presenting that right after the lunch break. Again, I am specifically interested, as I said, in any type of analysis to see if some of the pre-entry characteristics of the patients had any impact on the outcome; also, whether wound size had any significant outcome effects. Lastly, the other thing that I think both Dr. Norden and I mentioned is if you have any data specifically on subtracting out the

eradication rates for those who were completely healed so that there was no ulcer, so that you knew what the eradication rates were in those patients where we have both a pre and a post culture.

DR. HOLROYD: Fine.

DR. CRAIG: So, as I say, I am just letting you know about those now. If you can do those and have that kind of information available after lunch, we will start off with you answering those specific questions.

DR. HOLROYD: Thank you.

DR. CRAIG: Any others?

DR. MURRAY: Yes, I don't know if they can look this up particularly at noon but I have heard some concern about what would be the cure rate if there had been a placebo arm. I understand that decision was made a long time ago, but if there is some debate or some discussion addressing that issue.

DR. CRAIG: All right, let's take our lunch break and then we will meet back here at 1:45 and start promptly.

[Whereupon, at 12:35 p.m. the meeting was recessed, to be resumed at 1:45 p.m.]

AFTERNOON PROCEEDINGS

DR. CRAIG: We are going to begin with Dr. Holroyd, who will address the questions that we had previously. This will probably take somewhere in the range of about 10-15 minutes to address all the ones that were presented.

DR. HOLROYD: Thank you, Dr. Craig.

[Slide]

What I would like to show first is just some rather simple-minded exploratory analyses, looking at whether people had some of these clinical cofactors we talked about this morning, yes or no, and how the clinical response rates came out for end of treatment and follow-up for the two studies. Then we will address what we have done on an exploratory basis for several logistic regression models for these type of cofactors. This will be all told about eight or nine slides.

This is similar type of data presentation of this simple-minded analysis of some of these cofactors. What we have done is shown some data here for the two studies, the overall clinical outcome, that is resolved plus improved percentage by history, yes or no, of having this history of a prior amputation. This is in the intent-to-treat group.

Shown here for study 303 and study 304 are the response rates and numbers for pexiganan and ofloxacin for

people that, yes, had a history of osteomyelitis or, no, they didn't, both at end of treatment and end of follow-up. Again, this doesn't take into account by itself the many complex variables interacting in the clinical response, including all the ancillary treatments of debridement and pressure off-loading and good ulcer care which we tried our best to standardize.

However, we can see, I believe, that there is a trend for this one yes or no variable in study 304, that there was a difference in the clinical outcome rate -- these point estimates -- for people who did have this history compared to people who did not have this history between pexiganan and ofloxacin. There was a point estimate of a 4 percent difference in the no group at follow-up. There was still a difference at follow-up in the 303 study for this cofactor.

You will note that in the 303 study ofloxacin had very similar point estimate rates of the clinical response whether this history was present or not. In contrast, in the 304 study you will note that pexiganan for these patients in this study, with this history of amputation, had little difference in clinical outcome, 4 percent positive, 5 percent negative, between end of treatment and follow-up, and ofloxacin had a point estimate 8 percent lower and 10 percent lower for patients with this history of

osteomyelitis. Obviously, these data are complex and many variables are contributing to any of these outcomes.

[Slide]

If we look at the microbiological overall outcome, infection resolved plus improved, we can see that in general the microbiological response was reasonably comparable between the two treatments at the two time points for the two studies.

[Slide]

Let's look not at some of the other cofactors that potentially could influence clinical outcome. Here is history of osteomyelitis. Again, this was slightly greater in the pexiganan 303 study group as a history. We see here that in the 303 study the clinical outcome at the end of treatment and at follow-up tended to have a lower point estimate for people with this history.

In the 304 study this was not the case, with it being slightly higher in the pexiganan group. In the ofloxacin group there was little difference in 304 at the end of treatment and, like the amputation history, the point estimates at follow-up were about a 9 percent difference for ofloxacin -- again complexity here.

[Slide]

Let's look now at overall clinical outcome at end of treatment by gender. We see here again, and we just made

a simplified version of this slide during lunch so I apologize that I don't have the exact numbers of individuals but we will remind you that about three-quarters of the individuals were men in the 303 study and about two-thirds in the 304 study, and that these were pretty well matched between the two treatment groups.

We see here that at the end of treatment men compared to women tended to have a slightly lower point estimate of the response and at follow-up, however, in the 303 study this really was not evident.

In the 304 study, particularly for pexiganan, we see that the response rate was quite high for the one-third of women in the study, relatively lower for the men, and for ofloxacin I would say they are reasonably comparable, slightly higher point estimates for the men.

I think what we can say for this history of osteomyelitis and amputation, in a simple-minded way from these type of analyses, that there are many things contributing to clinical response. Among the patients in the 303 study with this history pexiganan tended to have a lower clinical response for people with this history of amputation, and in the 304 study ofloxacin tended to have a lower response for people with this history. The imbalance was for the people with the history in the 303 study.

[Slide]

Let's look now at overall clinical outcome by baseline wound quartile. What we have done is just divide the baseline wound areas into quartiles with the fourth quartile -- I just want to confirm with my statistician because I actually didn't ask him at lunch -- that is correct? Yes, I just wanted to confirm that before I said it. The fourth quartile are the largest wounds at baseline, the first quartile are the smallest wounds at baseline. This is for 303 at the end of treatment and follow-up.

The numbers are the numbers, obviously. This is exploratory analysis. I think that in this study the differences in the point estimates of response varying by ulcer size did not differ significantly across the ulcer size quartiles at baseline. If anything, they are actually closest in the largest ulcers at baseline.

[Slide]

In the 304 study, we have here again the clinical response by baseline wound area quartile. We can take a look at this data. I will leave it up here for a few seconds, or longer if anyone wants me to, obviously. I think that it is hard, at least for me, to really discern too much of a trend, other than maybe at follow-up where there could be a slight trend where the first quartile does a little better, but I can't make much of it.

[Slide]

So, taking these kind of simple-minded exploratory analyses, we have recently submitted this information to the agency but there hasn't been any great discussion of it -- our statistician, Mr. Howard Height has considered an exploratory analysis to look more formally at these concomitant variables, and we have used the 0.05 significance level as a criterion as a guide to present these results.

These were performed in each study and across both studies. We looked separately at end of treatment and follow-up clinical response. We looked at models that included the treatment, the history of amputation, history of osteomyelitis, gender and baseline wound area. Fixed models were fit with no stepping procedure for these groups of variables run separately.

[Slide]

I will just summarize briefly the results here. For study 303 in a model containing gender, history of osteomyelitis and history of amputation no individual factor was found to be significant for the 0.05 level.

For the model containing gender, history of osteomyelitis, amputation and baseline wound area, prior amputation and baseline wound area were borderline significant at end of treatment but not at follow-up.

Models containing treatment with the above showed

that treatment was the greatest contributor to the response. In study 304, no individual term or pattern of terms approached significance.

That concludes my presentation on this topic. I would like to just address briefly several other questions or take any questions on this, and then I am asking Dr. Lipsky, if that is all right, to make several comments addressing questions about what information there is or what speculation there would be about potentially placebo, that is, non-antimicrobial therapy for these types of patients, and some of the other questions that people asked.

DR. CRAIG: Any questions on the material shown so far? Dr. Archer?

DR. ARCHER: Yes, I have a question that is not exactly on this but I was trying to get an idea about the wound infection score. Can you just give me kind of an idea about what was the highest wound infection severity score that was admitted to this study, and what would that wound look like?

DR. HOLROYD: Well, I am trying to figure out what I can say exactly about that, Dr. Archer. I know the scale goes from 0-21, just to bracket things a little bit, and the average score was around 7. The highest score I actually don't know off the top of my head. Maybe Mr. Height can help me out here. If someone has a copy of my talk, I may have

some ranges in my talk presentation from this morning.

DR. ARCHER: I am trying to get an idea of the limit of erythema around the lesion and the amount of pus to try to get an idea of what the bad ones looked like that were treated versus the ones that weren't so bad.

DR. LIPSKY: Maybe as one of the investigators that enrolled some of these patients, I could try to address that. In terms of the limits of erythema, we chose arbitrarily a 2 cm cut-off. We thought it was fairly easy to say a little less than inch and most people would understand that. They often do come in with purulent material but it gets cleaned up so that what they look up when they first came in, if you took a photograph few would doubt that that was infected. By the time you cleaned it up, sometimes it might look uninfected at that point. But most of these wounds would have looked similar to the ones that I showed you. They were through full thickness skin ulcers, epidermis and dermis; did not penetrate into subcutaneous tissue; usually did have a rim of erythema, and almost all had some purulence. They came in saying, "I've had this ulcer for a while but now it's gotten worse." So, one thing about foot ulcers, especially in a VA hospital like my hospital, it is not the presence of the ulcer that brought them in but, rather, that the ulcer is now infected in their view and in view of the investigator.

DR. ARCHER: What would a 7 look like, the average?

DR. LIPSKY: I think the first of the two slides I showed you would probably have been a 7.

DR. ARCHER: Thank you.

DR. HOLROYD: I would just note parenthetically that the standard deviation for the 7 was about 3.4. So, it gives you an idea of kind of the spread around the score, with the maximum being 21.

DR. ARCHER: Can I ask you another question? How well do the magainans penetrate into surrounding tissue? Do you have any data on that?

DR. HOLROYD: If I could have that slide, the last slide in our backup material? As I mentioned during my talk, about a month ago we became aware of a number of borane-based fluorescent dyes to which we could attach covalent pexiganan, and I showed the slide with the Staph. aureus. I just point this out, this is the only thing I can say that the most important point is that we don't have any good information about your question that is really terribly significant.

We agree it is an important question. Part of the difficulty in this area is that it is very difficult to quantitatively isolate a linear peptide in tissue which is itself made up of proteins and peptides. With this borane-

based dye -- I will be happy to show it if that is okay, we have done a grand total so far of one experiment, several weeks ago, where we placed it on a mouse muscle where the dermis/epidermis had been removed, I can tell you that in about two hours, as best as we can quantitate it, a 1 mg/mL concentration, so one-tenth of the 10 mg/mL in the 1 percent formulation, at a depth of a millimeter in one experiment -- so that is really all the information we have.

What we have done more in our development program, because of some of these difficulties, is develop the compound in a variety of ways, first collecting our clinical in vitro data, testing the compound ex vivo in skin infection models, testing the compound in infected swine wound models, doing experiments such as the translocated skin flora, and then ultimately seeing how effective it was. But the penetration information, we agree, is a very important question but that is about all we know about it thus far.

DR. CRAIG: Yes, Dr. Danner?

DR. DANNER: Does purulent material inactivate the drug? Do proteases metabolize it, destroy its activity?

DR. HOLROYD: We haven't examined this question in any detail. The studies obviously, as I showed you, were done in people where over 90 percent of the people at the baseline visit were debrided. It is a linear peptide. When

we looked at the decrease in activity, we saw, for example, I believe in the translocated skin flora study with the one-time application -- if I had to guess what may be going on, I think certainly through a wound there reasonably could be some absorption going on. We have seen some limited absorption, mostly of degraded material, with double-labeled pexiganan in animal wounds, and it wouldn't surprise me if part of the BID dosing regimen does involve gradual proteolytic destruction of pexiganan, but I don't have any data about that to directly address it.

DR. CRAIG: Dr. Miller?

DR. MILLER: Would you comment on the MIC for the Enterobacter? Enterobacter was the second most common organism. Is that correct?

DR. HOLROYD: It was Enterococcus.

DR. MILLER: Enterococcus.

DR. HOLROYD: Can someone get that for me? It is one of the early slides. Anyway, here are my comments about that. These are the data that we showed for Enterococcus for callus with the MIC-90 being 256 mcg/mL in the in vitro broth microdilution assays that these data were based on.

We would keep in mind that pexiganan is applied at this 10,000 mcg/mL concentration compared to the 256 mcg/mL MIC-90 value that we saw. In addition, we have the following other data on slide 33, and I will summarize it while they

are looking for it. Slide 33 of our backup slides.

[Slide]

This is the number of isolates that we have examined for Enterococcus specifically, looking at potential influences of different in vitro susceptibility testing methods for the in vitro MIC. What I can tell you is that for the broth microdilution assays we have in general seen little difference whether there cations were added to the Muller-Hinton broth or not.

For solid phase assays for pexiganan, which is also the case for polymixed ones, the agar assay tends to have allogenic acid and other negatively-charged components which bind pexiganan in these assays. In solid phase assays with agarose we have a lower in vitro mcg/mL value.

[Slide]

We also would consider that we have preliminary data showing that there may be some interaction in vitro between serum and pexiganan that could translate into the in vivo situation. I would point out that people like Dr. Jim Wilson, at the University of Pennsylvania, have looked for the interactions of antimicrobial peptides, published in The Journal of Clinical Investigation.

[Slide]

Finally, we have looked, again in an ex vivo pig skin model, where we take 5 times 10^6 bacteria on the

surface of the skin, incubate and sample.

[Slide]

Again, this is all just ancillary information which shows that we have on the left-hand axis a log reduction in the number of organisms for these different species in this model with increasing concentrations of pexiganan. We see that we do have evidence in this kind of ex vivo skin model of some anti-Enterococcus faecalis activity.

So all this is a rather long-winded way to say it is complicated with topicals, in my opinion, to draw conclusions about the high concentrations that are applied compared to the in vitro MIC values, and that there are certainly a number of additional factors taking place in the in vivo setting that also complicate this interpretation.

DR. CRAIG: Dr. Archer, did you have further questions? No? Dr. Murray?

DR. MURRAY: Just as a comment, about a third to a half of E. faecalis produce a protease so there are two proteases together. E. faecium doesn't produce it and I don't have any idea if that is the difference in the MICs between the two species, but it is possible.

DR. ARCHER: The question I was going to ask is are there any known protease cleavage sites within this 22-amino acid linear peptide sequence?

DR. HOLROYD: It is a linear peptide and it is certainly possible for proteases to cleave the agent over time.

DR. ARCHER: But you haven't looked for motifs? I mean, there are obviously specific protease cleavage site motifs for a number of proteases that are known. Have you looked to see if any of them are within this peptide?

DR. HOLROYD: I don't specifically know the correlation between any specific protease in the sites. I would certainly say that it is a linear peptide made out of naturally occurring amino acids, so it certainly would be subject to protease destruction.

DR. CRAIG: Dr. Lipsky was going to address the question about placebo results.

DR. LIPSKY: Thank you. I would just like to briefly address five issues that came up in the questions earlier.

[Slide]

The first question that came up is what percentage of diabetic foot ulcers might be infected, and we don't know that for sure but one of the sponsor's co-marketers of this agent did a small study where they asked 110 physicians who took care of diabetic patients who had foot ulcers -- about a third of them were primary care providers, a third podiatrists and about a third vascular surgeons -- to bring

their last five cases of diabetic foot ulcers into a session where they could look at what actual practice was.

You can see these estimates are the ones you have heard before, but the important point is that 40-80 percent of the last 5 cases that these providers saw were thought to have been infected, either proven infection by clinical and microbiological means, or suspected of being infected. They were then asked the question that also was raised by the committee, what percentage of these ulcers might actually be the type that you would be comfortable putting a topical agent on. About 40 percent were characterized as mild by a definition similar to that which I showed you; 30-40 percent as moderate. Many were called mild to moderate. About 20-30 percent were severe. So that is the closest I can come to unpublished data. I know of no published data that addresses this issue.

Let me address a couple of other issues that came up. One question I would like to address is about the distinction between wound healing and the cure of infection. I think one of the things that became a little blurred, at least in my mind, this morning was the discussion about what is the purpose of antimicrobial therapy. The purpose of antimicrobial therapy of an infection, of course, as the committee well knows, is to treat the infection. Secondary issues have to do with also helping a wound close because we

know that patients are better of with an intact skin envelope than an open ulcer. But that is not the primary indication. It would be like saying you treat a UTI to prevent pyelonephritis. You might want that as a secondary indication.

But the main reason for treating the local infection is because patients come in with symptoms of the infection, number one and, number two, because those infections can move to contiguous spread to cause deep soft tissue infections and, all too often, bone infections.

The second issue that was raised was about Gram stains. Over the lunch break we asked our statistician and microbiologist to review the data we had. We did do Gram stains on all of the cases because, as Dr. Reller pointed out, this is an important piece of information. At least we think it is. It was the intention that Ken and I discussed previous to this meeting to actually look at that in some detail because I am interested in potentially publishing that data because not much is available on the Gram stain in diabetic foot infections.

What I can tell you is that James grabbed the first 100 patients in the 303 study that were on the computer and, in looking at those, remembering that these specimens for Gram stain in culture were taken after a thorough cleansing of the wound, and then we scraped small

amounts of tissue and sent that in for Gram-stain culture, what they found was that about 12 percent of those specimens showed white cells and about 56 percent showed bacteria on the Gram stains. So, although it is a very small subset, it is the best we could do with the short notice on trying to answer that question.

The next one had to do with the issue of response to placebo. From the very beginning, one of the questions that I asked the company when they came to me to help design the trial was could we look at this agent first for clinically uninfected ulcers and see whether or not a topical antibiotic that reduced the burden of organisms might actually lead to better wound healing. We weren't sure that that is what we really wanted with an antimicrobial. So we developed a design that you have heard about this morning.

But we are left with the question of would excellent wound care alone, as Dr. Miller very nicely outlined, have led to cure in some, most or all of the patients that were enrolled in the study? I know of no data on this, and I have looked at the literature pretty carefully to try and address this issue.

What I can tell you is my own clinical experience based upon patients who come and say, "I had an infection last week and I was going to come in but I decided not to,

and it's gotten better," and data no better than those kinds of anecdotes. My guess would be that with excellent wound care alone, off-loading and applying appropriate bandaging and doing the debridement, perhaps 50-60 percent of these infections would have resolved -- just a baseline guess. That is in comparison to the approximately 85 percent that resolved with the topical as well as the oral antibiotic therapy.

Now, that may be a different response than Dr. Miller would give. That is based upon patients whom I see at a VA hospital. It is possible that patients at the Geisinger Clinic do a little better without antibiotic therapy or that you are a little better at your debridement techniques than we are.

I think that answers the questions that were addressed to me by the committee. Oh, one other question that came up was what about the issue -- I think Dr. Norden and Dr. Gerding both brought this up -- of patients who are unnecessarily treated with antimicrobials who really don't need to be because they are not clinically infected or, on the other hand, who are treated with a topical agent who might have benefited from a systemic agent.

I think that what happens is that a lot of physicians treat patients who have clinically uninfected lesions. I showed you the figure that 63 percent of all

patients who walk in and have a diagnosis of diabetic foot ulcer got an antimicrobial. On the slide that I just put up there from the focus group it also showed that 38 percent of those patients got a topical agent, and 30 percent of the patients seen by the primary care providers actually got a topical antibiotic. So we know that a lot of topical antibiotics are being used despite the fact that they have never been shown to be effective for this indication.

Also, if a doctor decides to over-treat, if you will, a clinically uninfected wound, I would at least raise the possibility that it would be better to over-treat with a topical agent that doesn't so disturb the microbial ecology, doesn't cause yeast infections and other secondary problems, doesn't cause systemic adverse events -- I think I would rather see over-treatment with a topical antimicrobial than the systemic antibiotic, recognizing that treatment of uninfected ulcers has never been shown to be necessary.

DR. CRAIG: Dr. Miller, would you want to comment on the placebo with debridement, what percentage -- I think the person who raised that question addressed it to you as well.

DR. MILLER: Yes. You know, I heard Dr. Lipsky's remarks and I would have to agree with him. I think that what he said is very valid. I don't have any figures at my fingertips. I would just point out that debridement is so

very, very important and these lesions can come in and they are malodorous, and they are draining, and you think you have a major infection here, and when you have debrided them the infection is gone. That would be the major point I would make. Indeed, these lesions do become infected but I would agree with what he says.

DR. CRAIG: Other questions? Dr. Murray?

DR. MURRAY: Yes, I was just going to respond by saying that I am sympathetic to the argument that it was just made, and I had sort of decided in my own mind last night that wouldn't it be better to treat topically with something like a magainan than an oral fluoroquinolone, based on the horrendous overuse that we are seeing with those compounds and, yet at the same time, I had a reaction. Do two wrongs make a right, and I am not sure, and I am not sure that either one of them is wrong, but I think, I guess, the FDA brought it to the committee was that we are not sure what is the percentage that would get better on their own, and is it 10 percent that really need a topical or a systemic, or 50 percent, and I think that is going to be the quandary.

DR. CRAIG: Dr. Parsonnet?

DR. PARSONNET: I was just wondering if there are certain center that contributed a lot of patients, and whether there were differences across the centers in the

results.

DR. CRAIG: Whether there was a difference across centers in numbers.

DR. HOLROYD: The largest enrolling center in either study, I believe, was in the 303 study -- I am forgetting my facts and figures here, was it out of 435 or so patients -- 493 patients enrolled; somewhere on that order, I don't remember the exact number -- 50 or 60 patients. That was a podiatry practice group in San Antonio, Texas.

We did look statistically -- I am not an expert at all on these results, for an outcome by center that you referred to. As we showed, there were about 80 centers that participated in the study. Some of them had low enrollment, and these were defined in the so-called pseudo-centers for this treatment by center analysis. I think the p value -- I can't remember, was supposed to be either 0.10 or 0.15 to show a significant interaction and it wasn't found. It was 0.15, Mr. Height tells me.

DR. ARCHER: One of the things that concerns me about the data a little bit may be part of the microbiological data. That is, there was a high rate of eradication in the ofloxacin group of organisms that we would consider not to be within the spectrum of that drug, such as enterococci anaerobes. Yet, they were highly

successful, which makes me wonder if that is a marker for how well these patients were doing with care other than antibiotics. I don't know, but that is a concern. I mean, I don't think we would think of treating enterococci infections with ofloxacin and expect success like this.

DR. LIPSKY: I think you are absolutely right about that, if I can make a comment. I think the best treatment for anaerobes is oxygen, and once you have removed the eschar, the full-thickness dead tissue and all of the materials that allow for an anaerobic environment using the kind of aggressive debridement that Dr. Miller showed, in fact, anaerobes disappear. That is one of the reasons why the odor goes away as debridement takes place.

Just speaking to the other issue around eradication of colonization, studies that we did looking at nasal anterior-nare staph. colonization found that fluoroquinolones are extremely active, much more so than penicillins, cephalosporins and other drugs at eradicating anterior-nare colonization. It is quite possible that when you put somebody on ofloxacin they stop shedding Staph. aureus onto the wound and when you put them on pexiganan they may not. So it just represents a different colonization of the wounds.

DR. MILLER: Would you clarify for me, in the protocol you did cultures at baseline and day 3, and then it

was the investigator's decision at day 14 or beyond. Right?

DR. LIPSKY: Right. I think they were encouraged to take culture at every visit if possible. The only reason not to culture was if the wound had completely closed or they felt that clinically it was unnecessary, and I suspect very few closed?

DR. HOLROYD: I believe that Mr. Bostwick from FDA or the statistical reviewer from the Division showed some of that data. Just to give an overall summary, it was about 20 percent of the patients in the studies. We also showed some data on percentage improvement and, again, as a rough figure, 50 percent of the people were cured clinically. The 50 percent that had the clinical response of cured, their mean or median percentage improvement in the ulcer was in the range of 70-90 percent. So a lot of these had closed a significant amount among those people.

I think this also may be related, at least in part, to one of the questions that I believe Dr. Craig was asking, and we did our best -- I don't have an exact figure to try to answer the question of how often the infections were resolved, responses, the results of an actual culture taken versus how often the result of a presumed eradication. I think, clearly, among these people where, again, the infection resolved response is about 40 percent; if your ulcer was closed, you know just as a rough figure, that was

20 percent of people; and there was no culture taken, and we consider those infections resolved. From the rest of the people, from what we can tell for at least the majority, overall among this 40 percent of people, did not have a culture result in their infection resolved, but I don't have an exact figure for you.

DR. CRAIG: Okay. Dr. Archer?

DR. ARCHER: One thing you might clarify for me also -- I wrote a note and forgot to ask, the cellulitis as an adverse event, did that mean that these people started off with a little bit of cellulitis and it got worse on therapy, or was this actually a topical reaction to the drug itself?

DR. HOLROYD: Well, that is a difficult question to answer. I believe Dr. Roberts outlined this morning that most people that had this adverse event of cellulitis did get additional antibiotic therapy. I don't have an exact breakdown but my impression is that clearly the majority of these cellulitis adverse events -- I guess 21 and 13 or something like that between the two studies, did involve the diabetic foot ulcer that was being studied. I think there may have been one or two exceptions but I don't remember.

As far as the distinguishing feature, I mean, I would agree that the cutaneous adverse event profile didn't highlight much of a difference in cutaneous adverse events

between active pexiganan, and there is really not a question, I don't believe, in the skin sensitization potential studies of the vehicle being a sensitizer; it is more likely the vehicle with the active pexiganan potentially. I think that the data on the cutaneous adverse event profile outlining very similar data between people who got the placebo cream and the active cream suggests to me, along with the information about these people getting antibiotics, that these were most likely real cellulitis events, not skin reactions. That is just an impression. That is what the investigators called it, anyway.

DR. ARCHER: My concern is that this might reflect the inability of the magainans to get into surrounding tissue. If somebody starts off with a little bit of erythema around the wound within your limits that you admitted to the study, it might blossom into a formal cellulitis. That concerns me a little bit about the use of this preparation.

DR. HOLROYD: The comment I would make there is that the overall number of adverse events for cellulitis, I believe, was 21 and 13. The osteomyelitis was slightly higher for ofloxacin, and the infection adverse events I think were 8-9 between the two studies, worse ulcer infection with ofloxacin.

In addition, I think, of course, an additional concern would be related to if these develop into serious or

severe cellulitis, and what I would point out there is that that was greater for pexiganan than for ofloxacin, however, seriousness and severity of osteomyelitis, as rated by the investigators, and for ulcer infection was greater for ofloxacin. So, that is the data.

DR. CRAIG: Could I ask a question? I think in the FDA's presentation they emphasized the decreased degree of wound healing that was observed with your compound compared to ofloxacin. One could interpret that as the drug was not as effective against infection and that is why that occurred. The other alternative is that one could say that maybe the drug actually had some inhibitory effect on wound healing. Have any studies been done in an animal model where one makes a wound and then looks to see if this compound has any slowing effect on wound healing? I mean, I think that has been appreciated with things like betadine and stuff like that that people have put on wounds. The drug may be very effective in clearing up infection but it also may have an effect of also slowing the wound healing a little. So, you get the differences were observed but, in terms of what you were looking at, purulence and all those kind of things, there was no difference. So, any data on effect on wound healing?

DR. HOLROYD: In animal models looking at pexiganan, I am not aware that we have any data looking at

wound healing with this anti-infective agent specifically. With other magainans, we have some not extensive experience looking at corneal abrasions, but not with pexiganan, where there was increased healing of corneal abrasions compared to control. There has been some interest in the academic community in trying to look at magainans as possibly promoting wound healing, but there is not very good data in my opinion.

I would point out that it is my believe, certainly for the 303 study, that the principal difference in the wounds's resolution, percentage or absolute amount of resolution, occurred principally in the patients who had clinically failed, and that there wasn't a great correlation between the clinical response and the improvement for the ofloxacin patients in particular. I think it also needs to be taken into account that debridement, which was taking place in a lot of these patients, can directly influence the wound area when you remove tissue and then measure the wound area. So, these are complexities.

As far as your other question, that is what we know. If I could make one more comment about the protease, I would also remind us that the pexiganan is placed in this one percent cream in a formulation where it is gradually released over time, essentially, from the cream as the cream penetrates and does it work. So, it is not like putting it

all on as a solution into the wound.

DR. CRAIG: Any other questions? Yes, Dr. O'Fallon?

DR. O'FALLON: I would like to understand the treatment a little bit better because, obviously, the evaluations were tied to the end of treatment and two weeks following it. It occurred to me after I heard it this morning that day 10 was chosen because originally the oral drug was approved for a 10-day treatment. Right?

DR. HOLROYD: That is right, although I would point out, as I am sure the Division would, that it is a little different situation where it is approved -- and the Division can help me if I am in error -- for a 10-day course of therapy and then the follow-up visit would be assessed after that. So, I think that was some of our original thinking, and that is why that was done originally but the therapy was actually for 14-28 days.

DR. O'FALLON: The oral as well as the cream?

DR. HOLROYD: Yes.

DR. O'FALLON: The oral was allowed to be continued for as much as 28 days?

DR. HOLROYD: Yes. I know I gave a rather rushed talk at the end, and I apologize. Both therapies were given for about 22.5 days, both the oral and the topical, as a mean.

DR. CRAIG: Any other questions of the FDA? Dr. Miller?

DR. MILLER: Can I ask one question about the wound infection score? Of the criteria, you have tenderness as one; pain is another and warmth; and induration. I am wondering, since I suspect most of these were neuropathic ulcers, how often did tenderness or pain come into play as a sign and a symptom?

DR. HOLROYD: It would take us a few minutes. We may be able to find how often that was there. I don't know if Dr. Lipsky would like to comment since he helped design the wound infection score, actually before I was with Magainan Pharmaceuticals, so he may have more perspective than I do.

DR. MILLER: I was curious why those criteria were chosen.

DR. LIPSKY: Just because we looked at what the cardinal signs of inflammation were, thinking that we were looking for the body's response to microorganisms suggesting that there was infection rather than colonization. So we just looked at all of them and we graded them. I agree with you that more often than not, because these were largely neuropathic ulcers, they had neither pain nor tenderness, although that was sometimes the reason that they came in with their infected ulcer. Did you have something?

DR. HOLROYD: No, I don't believe we do specifically. We had broken down a number of the components but I don't believe we broke that one down. I would point out that, as you say, there were about 80-85 of the patients in the studies who had evidence of peripheral neuropathy based on the monofilament and clinical exam, and about 10 percent had a history of no palpable pulses.

DR. MILLER: And the warmth was done with the back of the hand, just comparing one limb to another? Is that right?

DR. HOLROYD: Yes, I believe so.

DR. LIPSKY: Yes, that is the way it was done. Nowadays we have these wonderful skin thermometers that we certainly would have used them if we had them back in 1993 when we designed the trial. It was the back of the hand comparing one side to the other.

DR. MURRAY: I think this was already mentioned or I read it, but the question by Dr. O'Fallon brought it up in my mind again, the average duration of therapy was about 22 days and there was no difference between the two groups, whether they had been or oral active or cream active?

DR. HOLROYD: Yes. If you will give me a few moments -- I think it is 22.4 and 22.6 for extent of exposure.

DR. MURRAY: And that was physician driven, based

on their gestalt at the time?

DR. HOLROYD: That is correct. I will find the slide and show it to you in just a moment. I have it.

[Slide]

There is the data on the extent of exposure. This is for both studies combined. The number of patients is on the Y axis and then the number of patients at each of the assessment points that were on either the oral or the pexiganan cream therapy. The mean length of therapy was very similar between the two.

DR. MURRAY: Just one other question, and we have the decision not to check blood levels in humans -- that is something that FDA is comfortable with, and we probably don't need to worry to much about that?

DR. CHIKAMI: Yes, that is correct, based on the information that was provided during the drug's development process, based on animal studies and in vitro models of absorption across human skin, the biopharmaceutics reviewers looked at that, and that is correct.

DR. CRAIG: Seeing no more hands up, we need to go to the questions.

DR. CHIKAMI: Dr. Craig, Dr. Archer had a comment on the cellulitis as an adverse event, and we have looked at that, and this is just preliminary information that the company provided to us to get another look at this issue in

terms of adverse outcomes from potential failure in those patients who failed, either in the ofloxacin arm or the pexiganan arm, and the two outcomes that were looked at were infection-related hospitalizations and the number of amputations, and this is now for all patients enrolled during the study, and I just have an overhead.

[Slide]

This is information that the applicants provided to us earlier in the week, and these are basically tables provided from line listings. These are clinical failures at follow-up for the intent-to-treat population for both study 303 and 304.

In the upper panel, for pexiganan there was a total of 58 failures. Of those, 13, or 22 percent, required an infection-related hospitalization; 3, or 5 percent, had an amputation during the study follow-up period. For ofloxacin there was a total of 39 failures. Nine, or 33 percent, had an infection-related hospitalization and 5, or 13 percent, had an amputation.

For study 304, in the pexiganan arm there were 30 failures; 4, or 13 percent, had an infection-related hospitalization; 4, or 13 percent, had an amputation. For the ofloxacin arm, there were 26 failures. Seven, or 27 percent, had a hospitalization; and 3, or 12 percent, had an amputation.

DR. CRAIG: Thank you, Dr. Chikami. Any other comments that you wanted to make? No?

Committee Discussion

[Slide]

DR. CHIKAMI: What we have is an overhead of the questions that we would like to discuss. I think in general many of the issues that the Division sort of has been considering have been touched upon in your questions and discussion after the presentation and early this afternoon, after lunch.

I think the issues that you briefly talked about are the patient population that was studied in these trials; what is the sort of role of antimicrobial therapy in these patients; and, more specifically, what is the potential role for a topical agent in these patients; and how would one appropriate define the patient population for which a topical agent might be appropriate.

Then the other issues that have been touched upon are sort of the overall assessment of the clinical data, not only the clinical response but other endpoints that have been discussed -- not only the measurement of wound scores and the change in size of the wound, how relevant is that to your overall assessment, and also, as was importantly pointed out or discussed, the microbiologic assessments -- what do those tell you about the effectiveness or the

utility of such a product in the overall treatment of infected diabetic foot ulcers.

So, I will just briefly review the questions and then stop there. The first question is discuss your assessment of the data presented regarding the safety and effectiveness of pexiganan acetate for the treatment of infected diabetic ulcers. Please address the following:

In addition to the overall clinical response, which of the secondary parameters do you feel are important to the evaluation of its effectiveness?

Part (b), please address the potential risks and benefits of pexiganan acetate's clinical use for the proposed indication in the population studied.

The second question is based on the discussion of the above, do the data support the safety and efficacy of pexiganan acetate?

If yes, in what patient population should the drug be used?

If no, what studies would you recommend that the applicant conduct to provide further evidence of safety and effectiveness?

DR. CRAIG: Thank you. Just for everybody, if they have Dr. Bostwick's presentation, I think on the third page of that, slide number 13, there are listed the various secondary efficacy parameters. We can make sure that we

touch every one of those in making our assessment. But, clearly, the question is in addition to the overall clinical response, which of the secondary parameters do you feel are important to the evaluation of its effectiveness? The first one that is listed there is microbiologic response. Comments from people as to microbiologic response? Dr. Norden is ready to respond.

DR. NORDEN: I think that I have never liked it as a part of most of the studies, partly because of the issue that we weren't able to get a clear answer to, which is whether it is tied to the clinical response, which it often is, and nobody gets a culture, and so we say the organism is eradicated. I am not sure that it is terribly helpful to me here.

The second point is we know there are lots -- not lots, there are clinical situations, certainly, where the organisms persists and the patient does fine. And, with Klebsiella pneumoniae you can recover the organism for days after the patient is improving and the patient is not a failure. So I am not convinced that microbiologic response is terribly helpful, and here distinguishing between infection and colonization I think is very difficult.

DR. CRAIG: Dr. Murray?

DR. MURRAY: Yes, I agree. I think it is something that I am interested in seeing in the context of is the

organism that was originally there still there and now resistant, in which case you would need to do strain typing to make sure it was the same organism and not a new colonizer. So, in that context I would be interested, particularly if it was appropriate for a drug known to have mutational resistance.

DR. CRAIG: Yes, Dr. Archer?

DR. ARCHER: I just want to second and third those comments, and the fact that there are a lot organisms that are called to be part of the flora of an infected diabetic foot that are not covered any of the drugs that are used -- and we could name a whole raft of them, yet they do fine. So, I don't know that there is any correlation between the microbiological culture result and clinical response. So, I was also not terribly impressed with this. I agree.

My problem also is that frequently we don't do any quantitative cultures so that with the skin, that is an area where we have even had an advisory committee meeting on that before, and just recovering the organism doesn't tell me that the organism hasn't been significantly reduced in numbers, which, in my mind, would be a more positive aspect. So, you might see it reduced in numbers but if you are just looking at whether it is there at the beginning and there at the end, you might not see a difference.

DR. CRAIG: Yes, Dr. Rodvold?

DR. RODVOLD: My other concern, and I agree with everything, is that it leads you to want to put it in the label, and you are going to have a listing in the label that will have all these organisms that were recovered and I think it gives people false security potentially. So, I agree with the other statements but it also leads to labeling issues that I wouldn't want to see.

DR. CRAIG: Although here if it was included, that false security might be the opposite effect since it looked like there was a little less elimination with this compound compared to the comparative agent. Any other comments on that?

[No response.]

So, am I seeing the group sort of saying microbiologic response isn't very important? Do you agree, our new member from Duke, Dr. Reller?

DR. RELLER: This is another situation where many are colonized; few are infected after adequate debridement. And, the only endpoint I am interested in is an intact skin covering the previous ulcer.

DR. CRAIG: Okay. Let's move on to the next. If we don't think microbiologic is very useful, any bit push for combined microbiologic and clinical since, as everybody said, that is driven more by the microbiologic than by the clinical response?

[No response.]

How about wound size and depth? Specifically what you were looking at there was change in wound size and depth over time. Dr. Murray?

DR. MURRAY: I think that is kind of the endpoint that you are really interested in as an overall sense. I think it would also be important when a topical was involved to make sure, as you alluded to earlier, that it doesn't delay the process as well as potentially enhancing it with its antimicrobial activity.

DR. CRAIG: I see some head shakes. Do our consultants have any comments that they want to make? Dr. Miller?

DR. MILLER: I think certainly that wound size and depth should change. But if you look at the studies that we saw today, you know, there was no change, or very little change after the period of time but there was no consistent off-loading in these patients, and there was no specification as to where those wounds were on the foot. So, if you have a wound on the dorsal foot or the dorsal toe, they are easy to heal. But if you have one over the first metatarsal plantar head or over the heel or over the fifth metatarsal head, they are difficult because you must off-load those and they are the ones that are going to have the exuberant callus with pressure and friction. So, some of

them are very, very easy to treat and others you treat with difficulty. So, you must have these adjunctive measures going on as you treat with either a systemic or a topical antibiotic.

DR. CRAIG: Do we have any information on that? Was there any difference between the groups in that regard?

DR. HOLROYD: I don't believe so. We have a breakdown, Dr. Craig and Dr. Miller, where I can tell you that the most common group -- we divided it into four groups, plantar forefoot; plantar hind foot; dorsal lateral, on the top of the foot; or toes. The most common was plantar forefoot. I can show one piece of information here.

[Slide]

The second most common was toe ulcers, and then dorsum and hind foot ulcers were about equally shown. So, you see here broken down by these locations the clinical response. This is in the 303 study. Some experts tell me, I don't know if Dr. Miller would agree -- I think there is a slight trend for both treatments -- again, this is the 303 study -- for the hind foot having a slightly lower clinical response rate, and the dorsal lateral, the top of the foot ulcers, at least at end of treatment, having a higher one. Again, the numbers are small and the largest groups are the forefoot and the toes.

[Slide]

This is the breakdown for 304 among the different ulcer location types. I agree that for infected ulcers -- and I am certainly not an expert in off-loading techniques by any means, it remains a challenge during the infection period and afterwards as well.

DR. ARCHER: Am I to understand that the study design was such that in any one patient, if they had multiple ulcers that were eligible only one was treated? In other words, if they had three ulcers on the foot, one was chosen for treatment or all three?

DR. HOLROYD: Yes, Dr. Archer, the largest ulcer was chosen for the treatment ulcer to be followed during the study and the other ulcers, if they were considered to be infected by the investigator, were also to receive either the placebo cream -- whichever cream. I don't know if we have a whole lot of information on what happened to these secondary ulcers. I know it wasn't specifically captured.

DR. ARCHER: So, there is no data on comparison of the same patient on the same foot of a treated versus an untreated ulcer?

DR. HOLROYD: No. That is an interesting question.

DR. ROBERTS: All the ulcers that the patient had were treated with whatever cream they were randomized to. But, no, we don't have any data.

DR. CRAIG: So, I have heard so far from people

thinking that the changes in wound size and depth are important, with the caveat, as Dr. Miller talked about, that it is very dependent on where the ulcer is located as to how much healing one would expect. Dr. Gerding?

DR. GERDING: Bill, I think ultimately the goal is to try to heal these ulcers, and I realize that an antimicrobial is not exactly correlated with the healing of the ulcer but, rather, with treatment of infection. But I still fail to understand a systematic reason why there isn't as much wound healing in the topical group as there is in the ofloxacin group, and I am still bothered by that although I realize that that is not what the goal of an antimicrobial therapy is.

I still don't quite understand what the difference is. Maybe there is a difference because of this group that is failing, perhaps having enlargement of their ulcers or that group causing most of the difference in the amount of wound healing that is taking place. But you would also have to explain then why did those failures have more worsening than the worsening that occurs with someone on a systemic drug. So, I am still bothered by that. I mean, overall, I really think it is remarkable that a topical agent can do as well as this one has versus a systemic antimicrobial, but I would like to know, and I doubt we are going to find the answer today, why there is that difference in wound healing.

DR. CRAIG: Any other comments? Dr. Miller?

DR. MILLER: If I can get the data again on the breakdown of the location of the ulcers in those two groups, you know, were the dorsal skewed to the ofloxacin and did the topical get all the real ulcers on the plantar surface, or something?

DR. O'FALLON: Also the sizes. I mean, there is a discrepancy in the sizes.

DR. CRAIG: The question he is asking you is you gave us the numbers up there in terms of the ulcers but you didn't match up size with the ulcer. I mean, were the ulcers in certain positions larger than others?

DR. HOLROYD: I will make three very brief comments. First, why we showed by ulcer location, we showed by baseline wound area but I believe the clinical responses by the quartiles was similar. I don't have any data to answer the question if by location there was a difference in the mean or median wound sizes. I don't know if Dr. Lipsky has any comments on differences in sizes depending on the location in his clinical experience.

DR. LIPSKY: I think it is highly variable and I can't speak to it directly. In reference to Dr. Gerding's question, I would make one other point, which is that in addition to the fact that the outcome of the percentage reduction in wound size depended to some degree on whether

one looked at mean or median, and so on, bear in mind that we are also debriding these ulcers as we go along. So, an ulcer can remarkably increase in size, as you saw from the slides that Dr. Miller showed, between when the patient walked in the door, say, on his third visit and when he walked out. So, it is just a very highly variable number, with a huge standard deviation around it.

DR. CRAIG: But in terms of complete healing, if I remember right, the FDA did show that there was a difference between the two compounds, or not?

DR. DONG: Yes, there is a difference.

DR. CRAIG: Which page was that on?

DR. DONG: Page 19.

DR. CRAIG: So, the ITT percent of healed --

DR. DONG: It is 24 percent for the pexiganan group in study 303 and for ofloxacin it is 30 percent.

DR. CRAIG: That was not significant though?

DR. DONG: That was not significant.

DR. CRAIG: It only became significant when you look -- what is the difference with the other group there where you have percents with wound size increased or stayed the same? That was the only place where you saw a difference? Okay. So, in terms of percent wound healing, although it was less it wasn't significantly different. Is that correct?

DR. DONG: Yes.

DR. CRAIG: Okay. Next question going down the list, was the wound infection score. Yes, Dr. Archer?

DR. ARCHER: I think this is really critical, that is, which wounds should be treated topically and which ones should be treated systemically, and where is the border between the two? I think this is a real critical question. It seems to me that the wound infection scores were relatively low. These are relatively benign types of infections that may or may not have healed with good wound care. I mean, that has come up a lot and we don't know the answer to that. So, at what point is there enough wound infection to warrant systemic versus topical therapy? I think this is really critical. I don't know that there is any answer to that from this study but I think that is an important issue.

DR. CRAIG: Do we know, is there any correlation between the wound score in those that went on to develop cellulitis or needed to be hospitalized, looking at both arms? I mean, not just limited to your compound?

DR. HOLROYD: No, I don't have that data, Dr. Craig, I don't believe, breaking down cellulitis and the other thing you mentioned broken down by wound score.

DR. CRAIG: Dr. Gerding?

DR. GERDING: I just wanted to comment on Gordon's

concern because I think this is going to be an indication that is an exceedingly narrow one, that you have to get it just right in picking your patients for treatment with this regimen, and it is not easy to decide between infection and no infection clinically, and it is not easy to decide when the infection is too severe versus just right for topical therapy, and I think that it will be important to try to generate some guidelines for the prescribing of a product like this, assuming that it is going to market. You know, with my experience with treating these kinds of infections, I would acknowledge that it is difficult, and I think Dr. Lipsky would as well. So, I think this will be a challenge for prescribers to try to judge this correctly in terms of who may benefit and not either over-treat or under-treat with a topical agent. So, I think that is a real challenge, and even experienced clinicians have trouble making the judgment.

DR. CRAIG: Yes, or in a way, actually getting down to one of the later questions about the patient population, but the question I still want to focus on right now is do you feel that the secondary endpoint using the change in the wound infection score is important for evaluating the effectiveness of this compound? I see somebody shaking their head. Dr. Gerding?

DR. GERDING: I think it is important. I think it

consists primarily of the kinds of criteria we use in differentiating an infected from a non-infected lesion. So, I think the change in wound infection score is an important parameter.

DR. CRAIG: And the speed at which they change so that, you know, they are similar with the comparator agent?

DR. GERDING: I don't think those parameters differed significantly.

DR. CRAIG: No, they didn't. I think they are important. That is what we follow clinically.

DR. CRAIG: Okay. I see Dr. Norden shaking his head. Anybody else feel that it is a useful test? Dr. Miller?

DR. MILLER: I would just comment again on the particular criteria that you have for the score, and Dr. Lipsky responded to that, you know, as far as the tenderness and the pain in the neuropathic foot. It has been my experience that when people with neuropathic feet get pain in an ulcer, frequently it is a more serious infection than just something that is superficial.

I would ask about the induration criterion. You know, when you have a markedly deformed foot sometimes induration would be hard to appreciate, plus, these people tend to have stiff joints and their collagen tends to be stiffer also. So, you know, I am not sure. I am thinking in

my own mind how I would evaluate that to say, yes, this is indurated and this corresponds to the infection, and then we can become more sophisticated with the warmth, more than just a guess, if we really have a measuring stick.

DR. CRAIG: I am a very strong believer that we need to do more of this in a whole variety of clinical infections because there may be differences, agreed that they may be minor but they may be important differences clinically, and if we don't have some way of trying to get a little bit more objectiveness into our clinical assessment it is hard to do. I think the FDA pointed out, at least looking at the data here, that all of the components within this score did change with time, although there was some difference between the two compounds specifically in the wound healing or the reduction in size. Dr. Murray?

DR. MURRAY: Yes, I just wanted to comment, those of us who are just sort of shaking our heads, nodding yes -- I mean, yes, it is my impression they seem to be useful. Does that mean that I am convinced that every single measure listed under these scores is useful, no, I am not, and I think if you wanted a better opinion on that, if you are really going to sanction it, then you want a panel of doctors of Millers and Lipskys to comment as well.

DR. CRAIG: Yes, Dr. O'Fallon?

DR. O'FALLON: I have never done this of course,

but I have worked on scores for other complex situations such as quality of life, and the problem here is that everything in there may be very important but they may be interrelated to each other and they may not be of equal importance. So, this type of a measure really does need to be validated. There has been some work on it, according to the packet, but has it really been properly evaluated to see whether it is a good measure?

DR. GERDING: In studies that I have done we have not used pain, tenderness and induration, which are the things that Dr. Miller is also raising. So, it probably is worthwhile to look specifically at those three at least in terms of how much they follow the other parameters in terms of contributing to that wound score. At least for me, those were the three that caused me the most concern.

DR. CRAIG: Dr. Reller, you look like you are about ready to say something?

DR. RELLER: To carry this just one step further, with different values of the components of the score it may also be related to where the ulcer is. So, induration may be worthless for a plantar but not for a dorsal ulcer. But to get that refined in how it correlates with wound healing seems to me to be very important because you could develop possibly a score that would give guidance to who should be treated with any compound that might ultimately be approved

for this specific indication. That a compound would work when there is infection but not too much infection I think is just too fuzzy to get proper targeting of an approved compound. So, to get the scores validated and simplified to the ones that really do correlate with wound healing would be very important, and there may be appreciable data, just not analyzed, already as a starter that is already in the packet, which just hasn't been looked at that way.

DR. CRAIG: Any other comments? And, we are talking here only about the wound infection score which, obviously, people have said is important for deciding the extent of infection, but how about the total wound score which also includes pulses? Does the same thing apply? There were two of them that were used. There was one that was an infection score, primarily to look at the extent of infection and to follow that and, again, that would be the component I think the company would be talking about, that there drug is effective and that total wound score might not necessarily be the primary indicator that should be looked at because that takes also wound healing and wound measurements in there, and that could be something else besides related entirely to infection. So, I am trying to find out is there any differentiation, and for approval do you feel they are both equal, or do you feel that one carries a little bit more weight than the other? Dr. Norden?

DR. NORDEN: I think that the wound infection score carries more weight, and the other is even more complex when you start looking at the pulses, the circulation and so on. So, if we could refine wound infection score I would be very comfortable without having to worry about bringing in other variables.

DR. CRAIG: Dr. Gerding?

DR. GERDING: I agree with Dr. Norden. In fact, I had a lot of difficulty with that overall wound score in terms of trying to figure out how you would do that, and things like brawny edema and pitting edema and duration of the ulcer. It may be useful as a means of teasing out differences in outcome perhaps if you have that kind of data, but when you mix such disparate variables as pulses present, pulses absent, duration of ulcer and brawny edema, I have a hard time trying to sort out a unified concept of what that score means. Individual variables may actually be better, such as duration of an ulcer, in teasing out some kind of an indicator of success or failure in the management, but I have a hard time with the overall total score that is being generated.

DR. CRAIG: Okay. Dr. Reller?

DR. RELLER: I would like to ask Dr. Miller if there is some role in at least some components that went into the total score to be used to delineate those patients

who you would not expect to benefit from this therapy, moving toward the selection of patients. But if there are those who have findings that would preclude a response, even if infected, by the other score, then that would seem to me to be important to delineate.

DR. MILLER: Yes, certainly we are dealing with many different factors here, and pulses are very different from brawny edema. I think if a patient comes in for the first time with an infected ulcer and meets the criteria for infection, you know, the first thing that has to be done is that the person has to be evaluated from a vascular standpoint. You know, does he or she have pulses and, if not, what is the severity of the peripheral vascular disease because something will have to be done about that otherwise it won't matter what you do with the infection. Then, also, what is the status of the neuropathy.

So, I think the two things that you are evaluating, the sine qua non, are to evaluate the peripheral vascular system primarily and then what is the degree of neuropathy.

DR. CRAIG: Just to summarize what I think I have heard, and people can obviously correct me if it sounds more like my own impression than that what you said, it is that in terms of the secondary parameters which were felt to be important in evaluation of effectiveness, microbiologic

response was not felt to be one, neither was the combined clinical and microbiologic because it is really driven a lot by the microbiologic response. Change in wound size and depth, especially complete healing, was felt to be an important secondary parameter. The wound infection score and its change over time was also felt to be an important indicator, and lastly, the total wound score much less so because of the variety of other factors that could affect it. Is that sort of the gist? Dr. Danner is going to correct me now. Go ahead.

DR. DANNER: I guess what I thought maybe some people were indicating is that the infection score would be important if we knew whether it was useful or not. It hasn't been validated, from what I have heard, and it has to be prospectively validated in some way and be shown to correlate with anything. You don't know what it means. It is great to have one, and to have one that is prospectively validated. I think everybody agrees with that. We just don't know about this particular one.

DR. CRAIG: All right. So, again, right now people are interested in it but the question is whether this is a valid one, as has been raised by the committee.

Let's move on then to the second question, the potential risk and benefits of pexiganan acetate's clinical use for the proposed indication in the population studied.

DR. CHIKAMI: Can I make a comment, Dr. Craig?

DR. CRAIG: Sure.

DR. CHIKAMI: I think we would like to have you discuss this in the overall context of the discussion you just had, that is, as you have looked across these studies and you looked at not only the primary clinical endpoint but these other sort of analyses that have been done and sort of commented on how important you think these are, how useful these are, and as you discuss part (b) which is related to your sort of overall assessment of the potential risk and benefit of the use of the product, keep in mind sort of what you commented on under part (a).

DR. CRAIG: Dr. Norden?

DR. NORDEN: I am not sure if this is just going to address part (b) but because I have to leave at 3:30 -- I have a lot of trouble with this whole study and this whole concept, the whole concept of a topical agent, partly because, first of all, I think the company has studied a lot of patients; I think the trials in general are well controlled, well done as far as I can see. I think they are competing with the comparator agent is a very difficult agent to show equivalence to. I would just remind everybody that the 15 percent lower border of a confidence interval is arbitrary, and may be valid and we may have to set some standard but there really isn't anything magical about it.

Despite saying that, in general, if you look at the clinical responses, if you look at the change in ulcer size, the cream did not do as well as the systemic agent, ofloxacin.

Finally, I would just like to add that I am amazed that there weren't more dropouts in the ofloxacin arm. Taking it is not benign. We have seen some rather miserable reactions, including central nervous system type reactions in patients we have given cipro. or ofloxacin to. And, I think there is something very tempting or appealing about the idea of having an alternative therapy, but I think either Barth or Dale summed it up correctly, to find the population in which I would want to use this agent is still what I am having trouble with. So, I am really on the fence at this point.

DR. CRAIG: It was interesting going through and looking at the names of the investigators. You do see some infectious disease people, but the numbers of cases entered at those places are relatively small, and most of them are coming from podiatrists, clinics that deal primarily with feet. It may be that those of us in typical infectious disease practices really aren't seeing these patients since when they get referred to us is when they have not responded to the other things. So, our own vision of what we normally see is not what is really out there in the community. At

least, that is the gist I got from looking at the data because, you know, there are very small numbers from people who are working in typical infectious disease practices bringing the people in.

Again, if it is 40 percent of them that are mild ulcers, this could be a significant number of them in the regular communities. So, I think we have to be careful of using our own day-to-day experience in our own practice. It may be entirely different than the real disease, this milder disease that is going to be treated.

DR. NORDEN: I agree with that, but I think we need something better than either the list of things that the company proposes which they would not treat, and trying to define whom you would treat. I mean, it is easy to say whom you wouldn't treat --

DR. CRAIG: Yes.

DR. NORDEN: With 104 fever you are not going to use a topical drug; bone showing through an ulcer you are not going to use a topical drug. But who are we going to use it for? Again, I am less concerned about Dr. Lipsky and Dr. Miller and Dr. Gerding making this decision than I am about a lot of people in practice.

DR. CRAIG: I can't remember, in their suggested insert did they have anything about the degree of erythema? I think if that is something that is primarily used in the

definition of your initial people you would probably be trying to do that; the same thing if there is a wound score as something that you are going to use that would help clarify the individuals a little bit more as well.

DR. NORDEN: It just says not extensive cellulitis.

DR. CRAIG: Yes. Dr. Murray?

DR. MURRAY: While I don't think the cream was as effective overall or equivalent to ofloxacin, I am probably willing to accept a little bit lower efficacy for the benefit of not having a systemic antibiotic and not eliciting or selecting for more resistance to fluoroquinolones. You know, as a well-known expert said it recently, we have blown it with antibiotics, and we could be in big trouble shortly.

As far as the potential for some of these patients developing cellulitis, while it would be possible that someone would get such a rip-roaring cellulitis and not come back to medical care that it would have its downsides, I think that is relatively unlikely. These are not people that are likely to be flying across the country away from medical care. They have already come in; I think they will come back if they get sicker.

So, at this point in time I would probably be willing to accept a slightly lower efficacy for the benefit.

I just wish I had a little better handle on what would be a placebo cure rate because I am not sure that we have actual benefit versus a placebo but I think we probably do.

DR. CRAIG: Dr. Parsonnet?

DR. PARSONNET: I don't think there has been any demonstration of benefit with this. I think that we don't have a placebo; that we don't know who these patients were who were selected as representative of ulcers in general; that when patients come to see their doctors they are not all randomized, that only a small sample is. The people that may have been randomized may have been the people who would have responded to placebo, and we don't really have any data for that. We really don't have any validation of the criteria that they used to choose people for this study.

So, I really can't say from the data that has been presented to us that there is really any benefit to this therapy, plus, we have been told that even as an estimate 50 percent of these people might have responded as a placebo effect, and that is taking sort of all-comers, not just people that were selected to be randomized for this study. So, you know, I don't think there are terrible risks to this but I don't see that there is any benefit to this over good wound care, that that has been demonstrated to us.

DR. CRAIG: So, you don't see any benefits but you also don't see much in the way of risk?

DR. PARSONNET: I don't see much in terms of risk but there is cost. So, unless there are other data to show us who these patients represent, and that these patients really would do better than just plain wound care I can't -- I haven't seen that data.

DR. CRAIG: Okay. Dr. Lipsky?

DR. LIPSKY: Could I just make a brief point? The 50-60 percent figure that I gave was for patients enrolled in this study not for all patients that come in, jut to be clear about that.

Secondly, I would also ask you to consider the issue of another fluoroquinolone, for example, were applying for a specific indication for diabetic foot infections, they would presumably test themselves, say, against trovafloxicin. You would still not have a placebo-controlled study. You would say we are just as good as, or almost as good as trovafloxicin and, therefore, we would like an indication for diabetic foot infections. I think you are setting the bar unreasonably high to say that when we compare this product against what all concede to be a very good antibiotic for treatment of this infection, and it does almost as well, that that is not good enough.

DR. PARSONNET: I have one quick response to that. I don't think that it does really almost as well because if you are saying that 50-60 percent of these people may not

have required antibiotics at all, then the group that would have done almost as well is that 30 percent that is remaining. So, in fact, the difference that you are seeing between these groups is much smaller than the actual true benefit that is seen in patients who really need antibiotics. So, I am really not convinced from the data. We have so many people in here who may not have benefited at all from either arm of this therapy that you can't really compare -- you can't tell me what the real differences between ofloxacin and the topical are. So, I am just not convinced from the data that this is any better than placebo, and I am not convinced because I am not sure that the patients were correctly chosen to address that question.

DR. CRAIG: To take it just a little bit further, you mean because they were based on an infection score, or what?

DR. PARSONNET: Well, because I am not sure once they had debridement that they were really infected. You know, the infection score is a score that is done even before they are debrided, and once you have taken out the infection and thrown it in the trash I am not sure that you need any antibiotic.

DR. RELLER: Dr. Lipsky, if one got together a group of experienced clinicians who deal with these infections currently, recognizing, as I think you mentioned

earlier, that there has never been a placebo-controlled trial, what would be the agents be that a consensus group of experts would say would be effective in aiding wound healing, coupled with taking the pressure off, debridement, excellent wound care -- effective in infected diabetic foot ulcers as a part of their overall therapy?

DR. LIPSKY: So, if I understand your question correctly, in addition to good wound care --

DR. RELLER: Yes.

DR. LIPSKY: -- what anti-infective agent would an experienced clinician consider to be appropriate for treating an infected ulcer --

DR. RELLER: A consensus group, you know, not only just yours --

DR. LIPSKY: Right.

DR. RELLER: -- but, say, five experts together. I have my own list from what has been published, ad so on, but I am interested in seeing what you would come up with.

DR. LIPSKY: Sure. Well, if you ask me this about six to eight months from now I would be able to give you a better answer because I am actually chairing an IDSA group on developing guidelines for diabetic foot infections, and I intend to ask that question of the kinds of people you refer to.

My own feeling is that products should be tested

in the clinic in order for me to recommend them. So, I can tell you the agents that have been tested in studies: cephalexin and clindamycin have been shown to be 85 percent effective in treating similar type patients to the patients we talked about today, and either of them, it seems to me, would be a reasonable antibiotic agent. Trovafloxicin has certainly shown itself to be effective, and the comparator in the trovafloxicin study, Augmentin, or amoxicillin-clavulanate has shown itself to be effective. I think ofloxacin and ciprofloxacin have been widely used. I am a little more comfortable with ofloxacin the ciprofloxacin, although I think they have probably been overused. Levofloxicin perhaps would be a better choice. So if you ask me among the other quinolones besides trovafloxicin, perhaps levofloxicin would be the agent that I would choose. Dicloxacillin is still something that I sometimes use in a patient who has not recently had any other antibiotic and it is highly unlikely they have anything other than staph. or strep. but I don't often feel comfortable enough to just use dicloxacillin. I would be interested to hear your list and maybe have you sit with our group.

DR. RELLER: Well, my list was only the first four that you had down there. I ask the question because I would like to second some of the things that Dr. Parsonnet said. Dr. Gerding said he was surprised that this compound did as

well as it did, but ofloxacin is not approved for this indication. I recognize that at the time these studies were initiated the choices were more limited. So, I mean, you know, not to make too much of the point but I don't think it would be in the top tier of agents, and I have a nagging suspicion that these things don't look too dissimilar but if there would be any differences it is on the lower wound healing side. And, it may be that neither one is particularly good and, therefore, they don't look much different from each other.

What I would like to see is a validated wound score that was specific for the location, or correlated well and served the purpose for the location for this and other topical agents that may follow because the portion of the patients who would fairly be good candidates for such a drug are those that have some infection but not too much infection, and with a wound infection score, I think having a placebo-controlled trial to complement what has been done already is very important. If it is a lot better than the vehicle in which this compound occurs, or is applied, it shouldn't be very difficult with a validated wound score to show that. Without it, I feel I cannot, based on the data presented, say whether it works as well as nothing or not.

DR. NORDEN: Barth, my only disagreement, I guess, is that, again, the company did the trial -- well, let me

put it differently, if the lower confidence limit had not exceeded 15 percent in one of two trials, would we be sitting here and having a discussion? We might have a discussion about the labeling and so on, but we would have to say that the product met the standard that the agency has set up, I believe.

I am equally unsure that this is really better than placebo, but I am comfortable that ofloxacin is an effective agent, and I am comfortable that the numbers that we saw with ofloxacin in terms of clinical response are comparable to those which we have seen before with clindamycin and with cephalexin. So, I think there are certain reasons why I am uncomfortable with just sort of saying we ought to be doing a lot more studies. There are over 800 patients who have now been studied. So, I am not quite sure -- I don't think we would do a placebo trial because I would be very uncomfortable unless I could define the population very carefully and was not afraid of hurting them.

DR. RELLER: It just seems to me that to use this compound appropriately one has to have very precise indications for the patients who might benefit, and it is for that very reason that I am unsure that the difference with placebo in the very patients who could be narrowly enough defined would be legitimate candidates for therapy. I

mean, we want a forthright opinion and I am not very excited about it. I am sorry that there are over 800 patients but I am not very excited about the comparator and what we are trying to assessment from the comparator with the topical agent.

DR. MURRAY: I just wanted to say something about that because, in fact, whether people are using ofloxacin, levofloxicin or ciprofloxacin would basically have depended on at what period of time and what yoru pharmacy had bid to purchase. We switched from ciprofloxacin to ofloxacin for every infection strictly on what was bid to our pharmacy, and whether it was twice the MIC or half the MIC and twice the blood levels was not taken into account whatsoever. Did that make a difference? I don't know but I am quite sure levofloxicin has been widely used for this sort of infection. How effective it is I am not sure, but I am sure it would qualify as a standard of care.

DR. CHIKAMI: Dr. Craig?

DR. CRAIG: Yes?

DR. CHIKAMI: Can I just comment on that, just to follow-up on the conversation and what Dr. Norden had to say? I guess at the time these trials were designed, in fact, there were no approved agents with this indication. There was extensive discussion between the pharmaceutical company and the agency about what would be a reasonable

active control trial, and I think the discussions were in the setting that it was felt at the time that an active control trial was an appropriate design in this indication, and that it, in fact, may have been difficult -- and, again, I am trying to sort of paint the context of the situation of when these trials were designed, that an active control trial was an appropriate design.

Now, that is not to say that the issues that are being raised about what would, in fact, the response rate be in patients with very mild infections with good debridement and other sort of local care be, and I think it is very difficult to get a handle on that, as our experts sort of commented. Both Dr. Lipsky and Dr. Miller have commented that that number is very difficult to get a handle on. So, just to provide you with that perspective that, in fact, these trials were designed in discussion with the agency, and that with all of the limitations an active control trial was sort of the design settled upon, and that this was sort of the comparator agent that was felt to be appropriate at the time.

DR. CRAIG: Yes, Dr. Chesney?

DR. CHESNEY: Did you decide on a score of seven for some reason? In other words, if there was a score of ten were those patients automatically eligible for oral therapy or IV therapy?

DR. CRAIG: The score was not an entry criterion.

DR. CHESNEY: Not ever having seen diabetic foot ulcers, I wonder what is known about the natural history. I mean, would a score of seven normally improve without extensive therapy, or is anything known? And, why would it be unethical to use placebo? I saw that word somewhere and Carl indicated some concern about that, and I am just wondering why it would be of concern if the more seriously ill patients automatically got systemic -- I mean, they weren't included in the study.

MR. BOSTWICK: Not speaking specifically about this study but just historically, in the last few years we have had a difficult time getting sponsors to agree to placebo-controlled trials in infection disease processes unless it is a very mild -- impetigo perhaps. I think for reasons of liability they are reluctant to do it. So, maybe rightly or wrongly, we have kind of backed away from a placebo as a satisfactory control group, except in specific cases.

DR. CRAIG: Yes, you have brought it back for at least acute bronchitis now, that those have to be placebo-controlled, but that is the only one I know where you do require it. Other comments?

I personally think that ofloxacin as the active ingredient is not a terrible agent for Gram-positives and

for some of the anaerobes. Again, anaerobic coverage, as Dr. Lipsky's studies have suggested, is not that critical anyway, especially with debridement, and those things oftentimes are going to disappear on their own. So, I am looking more at the Gram-positive and the Gram-negative organisms and, in that regard, I think it is a reasonable agent. So, I did not have the trouble that you had, Barth, with the comparative agent.

DR. PARSONNET: Just one quick comment. I don't think that anybody would necessarily advocate a real placebo control but you are doing aggressive debridement, which is not exactly a placebo, and I think if you do aggressive debridement and you see at the end that you have actually got clean margins and things don't look very infected, and you try to take care of the infection by debridement, that may be actually a good control group to have, and then have the other group be a group that has the active agent. Because the question here is not whether doing nothing is the right thing to do; the question is whether doing surgery alone is adequate.

DR. MURRAY: I guess the same could be said for treatment of abscesses because if we drain most intrabdominal abscesses they may eventually heal in, but we wouldn't do it that way because antibiotics would facilitate the course and what we are saying is we really don't know if

they facilitate the course here.

DR. PARSONNET: You can look at this ulcer every single day and say is it getting worse or is it getting better. I mean, you are looking at it every day and you can make an assessment every day.

DR. CRAIG: But these patients were treated as outpatients so we weren't looking --

DR. PARSONNET: Yes, but they are looking at it. I mean, they are putting cream on it every day. You can tell them, "tell us if it's getting better; call us tomorrow if it gets red." I mean, they have an opportunity to look at it every single day, unlike an intrabdominal abscess which will come back and bite you, you know, if you are not taking care of it.

DR. CRAIG: Yes, Dr. Danner?

DR. DANNER: I think the problem here is this is kind of a tough one. You know, the data is not, in fact, clear-cut in either direction but, yet, on the other hand, you don't want to throw the baby out with the bath water, and you don't want to set new standards at this point which you are going to hold the drug to.

In terms of equivalence -- I think I agree with everyone here that efficacy is very hard to evaluate here. Equivalence has a clear statistical definition and that was what was attempted here, to do studies that showed

equivalence. From my understanding of the data, one study doesn't show equivalence and the other study shows equivalence though there is another difference between the two studies. In one study you sampled the data and you found that there were some discrepancies about how people would be rated, and it was like 18 percent. So, you redid the data and in redoing the data, it looked to me like it went against the drug, the pexiganan a little bit.

MR. BOSTWICK: But even if one used the original patient cohort it would have failed the per-protocol population. It appeared a little bit worse after we redid it but it came out pretty much the same.

DR. DANNER: In the second study there was a lower rate of discordance between your classification and the company's. It was only 10 percent.

MR. BOSTWICK: Correct.

DR. DANNER: But that data wasn't reclassified because it was a lower rate.

MR. BOSTWICK: Right.

DR. DANNER: But it seems to me that it is not inconceivable that if that data was redone it might either get stronger or weaker, and it might help us in some way.

MR. BOSTWICK: It may. I have no idea. We just set sort of an internal standard that if we found a 10 percent error we would accept that data. Another kind of reason for

doing the first study is that it seemed marginal to begin with. The second study seemed more solid and we thought, well, if we do find errors it is less likely to change the results. But we can do the second study and see what comes out.

DR. DANNER: I don't know how other people feel but since this is all so borderline, I guess I would prefer that the second study was reclassified just to see if it helps us in any way in terms of making a decision here, because I am not certain what to do. I guess, I ultimately think that the two interventions were not quite equivalent. They are close but they are really not quite equivalent, and if they are not really equivalent then, you know, it doesn't meet the original bar that was set.

DR. CRAIG: Right. But it appeared, at least in terms of background and wound size, that there were differences in that first study that were against this compound. So, the question is could those differences have explained the reason that equivalence was not seen. Were those patients that had those pre-entry criteria in those that had the larger wound sizes have a lower response and, therefore, because they were unevenly distributed between the groups, impact on the data. At least from the logistics analysis they did, looking specifically at that group, they couldn't pull out that that was a legitimate explanation,

although when you looked at sort of the dirty way of looking at it, there was a hint that maybe it might have contributed to it.

DR. DANNER: I may be incorrect about this, but even in the second study, the 304 study there was still the issue of wound healing and closure where the drug didn't look as good.

DR. CRAIG: Right.

DR. DANNER: That was in both studies. So, there are signals from both studies that maybe it is not quite as good, though I agree that the 303 study showed the biggest problem. So, I don't know. You know, it is just very fuzzy. I don't know what to decide but I guess since one study was redone and the other one wasn't reclassified and looked at, maybe we would get some help from that. Maybe the statisticians could tell me whether that is a reasonable thought or not. I don't know.

MR. BOSTWICK: We don't know. Basically, one of the things we thought about was that since 303 was done first the technique in 304, in terms of assessing patient results and just basically entering the data, was better. If I had to guess, I would say we would reclassify study 304 and still come out with the products not significantly different in the primary efficacy variable, but we can sure do it and see what happens.

DR. CRAIG: Yes?

DR. HOLROYD: If I may, I would just ask if this is a correct statement of Mr. Bostwick and the medical team, that the reclassification mostly involved having a per-protocol group where the follow-up visit window was emphasized as a criterion for being in the group, and that we emphasized end of treatment and day 10 visit windows, and your group included or excluded not based on those but on the follow-up visit window, and that was the principal difference for this additional per-protocol population in 303.

MR. BOSTWICK: Right, the principal reason for changing patients was visit window.

DR. CRAIG: Could we go on to the next one? I think this has summarized some of the risks I heard that some people voiced earlier, that this could go on and you might have a patient that didn't deserve to be on topical therapy and might have a cellulitis, but I think if you look at the data that was actually presented it didn't look, at least to my mind, that that resulted in a significant number of hospital days or an increased number of amputations compared to the people that were receiving the ofloxacin.

On the other hand, Dr. Reller suggest, well, they weren't on a very good system agent too, so that could explain why there were some patients that still, even with

that drug, needed hospitalization.

I think in terms of other kind of risks of resistance that did not seem a concern with the people. In fact, that was one of the benefits that I think I heard some of the people talk over some of the time that we have been talking, the ability to use an agent for which resistance has not developed as a benefit compared to a system agent where we have had experience with the development of resistance.

In terms of benefits, summing what I think I heard from the group, was that some felt there is something there, maybe not quite as good as seen with the comparator, to the response that this may not even be different than placebo. So, in terms of the benefits, I think the committee right now feels sort of from some effect to no effect. So, I don't think there is any consensus that I have heard as yet in terms of the response.

So, going on now, based on the discussion, do the data support the safety and efficacy of pexiganan acetate? Before everybody starts to disappear on me we have to get some votes or at least some comments on this. Carl, you are going to be leaving fairly soon so you had better get your comment in.

DR. NORDEN: I think the data support the safety; I don't think they support efficacy well enough to feel

comfortable. I think that the patient population is, for me, still the hardest thing to define, and I think it could be defined by a wound infection type score less than such-and-such. That needs to be validated, as people have said, which I think is where further studies would be -- I would feel comfortable if you could validate a wound infection score that I would use the cream in this population because I don't think it has to be equivalent to a system agent and I really don't want to keep on using ofloxacin.

So, I can't vote to approve it. I would not recommend approval at this point.

DR. CRAIG: But you are saying that they don't necessarily warrant more trials but more validation --

DR. NORDEN: Yes.

DR. CRAIG: -- of the patient population that one could use an infection score, or something like that, to identify the population.

DR. NORDEN: Yes. I don't really see going through the expense of another trial, either placebo controlled -- although I do think Julie is right. Would I feel comfortable using debridement only, vigorous debridement only and off-loading versus vigorous debridement, off-loading and the cream as a comparative trial -- that is intriguing, but I am still uncomfortable with outpatients. I know they are looking at it themselves but infection in diabetics can move

very quickly. That is not a "yes" vote I guess.

DR. CRAIG: Other comments? Do you want to add anything else, Julie?

DR. PARSONNET: No, I don't. I have to leave a little early also. I basically agree with everything Dr. Norden said. I feel that there is no evidence presented that this is unsafe. In fact, it looks like it probably is safe. I think that there has really not been any good data presented, to me, that indicates that it is efficacious, and I would love it to be efficacious because I would love people not to use quinolones to treat this type of infection if they could do something topically.

I would favor trying to do some sort of aggressive surgical debridement trial with very close follow-up of these patients, and whether you have the nurse go to their house every day to take a look at it or however you set it up, I think it would be helpful to have something like that.

I think there is a possibility actually that does have some risks to it that have not been mentioned because these people are now manipulating this ulcer every day. They are wiping cream on this ulcer every day, and that may actually have deficits compared to actually having it wrapped up in one of these protective boots for the span of a week. So, we actually don't even know from the data presented whether the cream has risks because some of the

risk to it may be related to something that they did in both arms of the study.

So, my sense is that it would be wonderful to show that this works, and I would be very enthusiastic about it if we could avoid oral therapy with these very potent antimicrobial agents, but I am not convinced by the data here that there is any efficacy shown at this point.

DR. CRAIG: Okay. Dr. Chesney?

DR. CHESNEY: I agree with Dr. Norden and Dr. Parsonnet. I also would love for this to work for the reasons that Dr. Parsonnet just said, that we didn't have to use very powerful broad-spectrum other drugs to treat. But I think with just a little bit more effort, even if it meant seeing the patients every day for the first few days and not just letting them make a report, it would be much more convincing to show that it was better than just debridement alone.

DR. CRAIG: Dr. Murray?

DR. MURRAY: Dr. Archer left his written comments that are in agreement with what has just been said. I guess I am perhaps going to be a minority opinion. I am going to say I think it doesn't look as efficacious as ofloxacin but I think it is pretty close to being equivalent to a standard of care. So, yes, I think it is safe. I think it probably is efficacious. It hasn't been shown fully equivalent in the

different studies but in one was. In what population should it be used? In relatively mild infection. If called to a vote, I would probably go with approval, or a recommendation for it.

DR. CRAIG: And what were Dr. Archer's comments?

DR. MURRAY: His were the same as the other three: yes, safety; no, efficacy; don't know if no treatment works in this group; what population -- very mild infection. Can physicians really make this distinction? What studies would you recommend the applicant conducting? Placebo-controlled.

DR. CRAIG: Okay. Dr. Reller, do you want to comment? Or, we can just take a vote of the remaining people, if you want to do it that way.

DR. RELLER: Well, I do agree substantively with what has been said. To me, one of the most important reasons for having a tight design with the wound validation score is that then one would have the objectivity to say this compound, with all of these other benefits for antimicrobial resistance, etc., actually works and doesn't have these other downsides. So, it just seems to me that one could make the case for using it much more forcefully if one had a database that would eliminate the concern that has clearly been shown about whether it works at all. So, it is the efficacy solidification, and we have two trials, one especially found wanting. So, I would not approve it on

demonstration of efficacy.

DR. CRAIG: Okay, but safety?

DR. RELLER: That is fine.

DR. CRAIG: That is fine? Okay. Dr. Miller, any comments?

DR. MILLER: I think from what we know at this point it does appear to be safe. I would just comment that, you know, there are those people whom you debride and they still have some erythema around. You know, they still have clinical infection and those would be the types of people that we would be talking about for this product.

I agree with Dr. Murray. I think there is some efficacy as I look at the trials, but there has been a lot of statistical maneuvering and I can't comment with any type of cogency on those because I just don't understand all of that. But I do think there is some efficacy, and I think it would be really good if we had a superphysiologic agent, as this appears to be, for use.

So, my concern is that patients can't evaluate themselves, especially this population. If you look at the data here, you know, they tend to be older. Many of them are heavy; many of them don't see well; and they can't see the bottoms of their feet. So, if you are going to evaluate something critically you really need someone to do it for them, and we see a lot of these folks and I just don't think

they are capable of doing that.

My concern is, like other products that are available, that, you know, people will use something like this without going through the other maneuvers -- without the debridement, the off-loading and checking the vascular situation. But I guess we would have to live with that. I would vote for approval.

DR. CRAIG: How is your feeling about a placebo-controlled trial? Do you think one could be done? Or, are your concerns that people can't see, and things like that --

DR. MILLER: I think if it were done someone would have to be looking for them, and I think someone should almost be applying the medication for them because I think compliance is a big issue. And, we are dealing here with non-life threatening diseases and I think the comment was made that, you know, you observe and if it looks as if something is worsening or changing then you intervene. So, it would require, I think, very close scrutiny. But that would be the ideal, certainly.

DR. CRAIG: You can't vote, Dale, but if you want to have any comment?

DR. GERDING: Yes, I will comment. I know I am not going to vote but I will tell you how I would vote. I actually would have added to Dr. Lipsky's list trimethoprim sulfa as an effective oral agent for treating these kinds of

infections. I have used it extensively. So, I would be completely comfortable with the comparator agent ofloxacin as being an effective treatment here.

I share everybody's concern about good debridement plus any kind of antimicrobial therapy versus good debridement alone as an efficacy test here. We don't have that data. I think the trial would be almost as big as the trial we have already witnessed here, the two trials, in terms of trying to prove that topical is going to be better than just the debridement alone. So, if you want that done, you are asking for a fairly large undertaking. That is my personal opinion because the numbers here statistically could be quite large before you were able to tease out the benefit of a topical, potentially at least, depending on how you select your patients.

I think the biggest concern I have is that the topical product failed to show equivalence in the primary outcome indicator of study 303. That, to me, is of most concern but I think it is showing benefit in these patients. That is my own personal opinion because we don't have a placebo or untreated trial here, or surgery alone trial.

So, I think it is advantageous. I would be inclined to suggest approval, although I must say I still don't know the answer to the questions that are being raised about how much we can do to treat patients without any

antimicrobial therapy. If these patients clearly met the criteria that were set here for mold infection, then I think they needed to be treated with an antimicrobial agent of some kind. I don't know to what extent that is true but we certainly saw an analysis in which we eliminated the low score, the people from the analysis, and I don't think that substantially changed the outcome. Correct me if I am wrong. You did do that, right? You eliminated the lower scoring wound infection patients in one of the analyses?

DR. ROBERTS: Four and less.

DR. GERDING: And that did not alter the outcome statistically. Is that correct?

MR. BOSTWICK: Slightly but it didn't make a statistical difference.

DR. GERDING: So, I think the product is efficacious. I share Dr. Murray's concern about inducing resistance with a lot of oral therapy. On the other hand, I am concerned about putting a topical agent on that may be used systemically at a future date and developing resistance to that too. So, that has both sides to it but I am inclined to think the product is helpful, but I am very concerned about how it will be targeted for use if approved; that it will be misused I guess is what I am concerned about.

DR. CRAIG: Dr. Parsonnet?

DR. PARSONNET: I hate asking the group to do a

placebo trial after they have done a lot of work already so I understand why people might be reticent to do that. And, I would like to suggest just one other alternative way to analyze the current data, if they have this available, and that is to look at the infection status after debridement and then exclude the people who really have no evidence of infection either after debridement or on day three so that you really have people who have infection once surgery has eliminated what it can eliminate. And, if there still seems to be fairly good clearance of that infection afterwards, then I would feel more favorable in terms of it being efficacious. If much of the effectiveness is due to surgery, or the predominance of it -- if the vast predominance of it is due to the surgery I think they would have to do a placebo trial.

DR. CRAIG: Dr. Rodvold?

DR. RODVOLD: Well, I have looked at this multiple ways coming in and while I have sat here, and I have probably come closest to Dr. Murray and Dr. Miller. Looking at the indication in a topical product for these types of patients as a consumer, I think with the data that it is safe. I think it will prevent potentially more increase of resistance because it is a topical.

The efficacy data is a little bit rocky but I think that in light of the number of people that potentially

would use the product, I am kind of favoring it. My stipulation goes back to the question I asked right in the beginning about mild, moderate and severe, identifying that, and I think that is really the problem that leads us to labeling issues here. The agency is going to have to come back to the score and try to come out with a score to lead people to identify and use that as a marker, or surrogate, or whatever to give people an idea of whether or not this is working.

In light of the trials that were set up and agreed upon, I think that is what pushes this forward. They agreed that this is the comparator, and I think ofloxacin is a comparator that is valid here. My concern though, like Dr. Miller's, is that people will start switching the order of treatment. The way the presentation by Dr. Lipsky was, was supportive therapy, surgical procedures and antibiotics being three, and it needs to stay still three despite giving a topical drug. And, I think it is very, very important that that comes across in the insert to people; that that information gets out there and is constantly brought to the surface.

If approval does occur, then I think they do need to come back and try to continue to help identify the right candidates and follow that, and continue to follow if resistance can develop at all, and not to stop where they

are at this point. So, I would move ahead with it.

DR. CRAIG: Okay. Dr. O'Fallon?

DR. O'FALLON: I was not very happy with the analysis because when I got done I had so many questions. When we try to do an equivalence trial, basically the idea is that we do it in the per-protocol. The definitive analysis of the primary endpoint is in the per-protocol, the reason being that you take out the people that didn't -- you know, presumably they were not treated per-protocol so all they are doing is diluting any effect, and they tend to make it look more equivalent because they move any real differences closer to each other. That is the philosophy behind doing it in the per-protocol.

Now, the problem for me right from the get-go has been the fact that there has been an unequal loss in those treatment groups. I am going back in here and there are as many as 21 or 24 more people dropping out of the cream active group as opposed to the oral active group in several of these analyses. That bothers me. Who went out? Who was left? We saw the baseline characteristics of the people that started the trial but we didn't see the characteristics of the people who were in the per-protocol comparison. So, we need more information in order to understand what we saw.

In the final analysis though, those definitive analyses said that this was not equivalent. That is the

problem, that the cream was not equivalent according to the standard analysis.

And, the magic 15 or 20 percent -- I think that is an FDA thing. In our medical center when we design equivalence trials, what we do is we sit down with the medical people and we say, okay, how much loss, how much drop in effectiveness would you consider acceptable given the cost, the harassment, the money, whatever it is, the bad things that are associated with the newer therapy? We set that and then decide what our level has to be, what the sample size has to be to have adequate power to detect that difference. I don't know, is 15 percent -- going from 75 percent efficacy to 60 percent, is that okay in this disease? Going from 70 to 55 or 50, is that okay in this disease? That is the bottom line in doing an equivalence trial.

As for the placebo thing, I came in here and there was a statement saying that it would be unethical to do a placebo trial and, yet, the first thing I hear this morning is that maybe there is a whole group of that don't need anything more than just debridement or, you know, surgery and good care. That sounds like maybe a placebo trial would be okay in a certain population. I don't know. That was a question.

DR. CRAIG: I think that was more or a "no."

DR. O'FALLON: That is a "no."

DR. CRAIG: Dr. Danner?

DR. DANNER: Could I ask three questions?

DR. CRAIG: Sure.

DR. DANNER: In terms of the animal studies that have been done, has a placebo trial looking at clinical efficacy been done in animals? I saw microbiologic data. Is there also data comparing this to placebo in an animal wound infection, that it cures the infection and that it is different than just giving wound care?

DR. CRAIG: I would ask the sponsor.

DR. HOLROYD: We conducted a number of infection models which I believe showed the anti-microbiologic efficacy in addition to the ex vivo studies of pig skins, a number of live animal studies with infections placed into wounds with Pseudomonas, Staph. aureus. Obviously, those are all so detailed data, and there was a reduction in organisms compared to vehicle, for example, if that is what you are asking.

DR. DANNER: No, I am asking if there was a clinical effect. You know, the fact that you reduced the number of organisms compared to, I guess, a placebo -- I saw that data, but if you give an animal a wound with a small surrounding cellulitis, is it different than just giving wound care?

DR. HOLROYD: As far as I know, we didn't do any kind of wound scoring system for these wounds in the animals at that time.

DR. DANNER: Okay. The next question for the FDA, you know, everybody agrees it is safe but what is not agreed on is whether there really has been a demonstration of either equivalence or efficacy. Is there a lower level approval? In other words, does it have to be efficacious? Could it be, like, you know, safe and may be a useful adjunct?

[Laughter]

MR. BOSTWICK: Dr. Chikami will answer that.

[Laughter]

DR. CHIKAMI: Thank you, Dave. The regulations speak to adequate and well-controlled studies providing substantial evidence for safety and effectiveness for the intended use. I think what you are getting at is what the intended use clause is. Under most circumstances, certainly for anti-infectives, in those situations where it is felt that a placebo-controlled trial is not ethical, in an active control setting we draw the conclusion that a product has demonstrated effectiveness and safety and the indication is what is called a first-line indication.

There are circumstances in other divisions within the agency where a product may get a second-line indication,

and this may be for a number of reasons. That has generally not been the practice within anti-infectives.

DR. DANNER: Okay. Then the other question, and I don't know if this can be answered, but are there other ongoing studies or clinical trials with this agent where approval for other indications is being sought? Can that be asked?

DR. HOLROYD: No, it is not.

DR. MURRAY: In their packet, they did use essentially a placebo in one study where they used gentamicin cream against a gentamicin organism but they were looking at wounds in swine that had organisms inoculated. They weren't looking at wound healing. In that case, where they used a gentamicin susceptible organism they reduced Pseudomonas. When they used a gentamicin resistant organism with gentamicin they didn't reduce Pseudomonas. That would essentially be a placebo but still just looking at bacterial load, not wound healing.

DR. DANNER: Thanks. I guess I think it is safe but I ultimately don't think you can, in the strictest sense, make the statement that effectiveness has been demonstrated. I think it probably does do something but I don't think it has been demonstrated.

DR. CRAIG: Okay.

DR. DANNER: Shall I comment on other studies?

DR. CRAIG: I might as well get my comments out first as the final person. In my looking at the trials, . looking at the primary endpoint, as I mentioned earlier, my one concern is with the one that did not show equivalency. Whether that could be explained by the abnormalities or the differences in randomization among the groups, although the logistic regression didn't clearly show that there were some suggestions. So, I am still not convinced that the reason that one did not meet that endpoint was because of the significant difference between the groups in some of those, the initial size of the ulcer and also the previous underlying disease.

I also am a little bothered by the data suggesting that t here is less healing, but, in my mind, can almost sort of dissect those two apart and say that they may be two separate things. And, what I would really want the investigators to do is actually to go to some animal models and see if these compounds actually do have any inhibitory effect on wound healing, starting off with an infected wound, to see if there is any slowing of the wound healing which would then account for the difference that was observed in both of the studies.

But in terms of its activity, I think the drug does have some efficacy. It may not be quite all the way to ofloxacin from that one study, but it is borderline, and

with the background, I would probably would have voted yes for efficacy and, again, yes for safety. But even with saying yes there would have been some questions that I would like the sponsors to answer. Specifically, the one that I would want to look at is if they could show any evidence that this drug had any impact on wound healing because, if it did, then that would make me feel even stronger that that was what you were seeing when you were looking at that as an endpoint, but that would be also something that you would want to at least put some caution in any package insert that the drug has as an addition to its anti-infective effect.

So, if we total those all up, I think it was four yes and seven no. Those are the numbers that we have sort of coming up. Although, I must admit, Dr. Norden's no was sort of a yes/no in that he didn't feel that they needed to do other studies but that what needed to be done was to standardize or validate the infection score so that he could look more at trying to ensure that the package insert identified the right subset of patients that this drug would be used for. So, no matter where we cut it, we don't reach a majority in favor.

Other studies that you would recommend to the applicant -- I think we have heard some. One of them was a placebo-controlled trial. How many would be in favor of that? Assuming it could be done?

[Show of hands]

There is a good majority on that, if it could be done. Obviously, it would be nice but I am not sure that it can be done. Yes, Dr. Reller?

DR. RELLER: Earlier Dr. Gerding said -- if I got this right, Dale -- that the numbers of patients that would be required to show a difference between placebo and this compound would be prohibitively large. Is that an accurate paraphrase?

DR. GERDING: Probably comparable to one of the studies that has been done here.

DR. RELLER: When one says how much would have to be done to show a difference tells me that it is all the more important to demonstrate a difference, particularly when we are talking about a very defined set of patients who might benefit. And, if they have no infection they are not going to benefit from an antimicrobial compound, presumably; and if they do have infection they can have so much infection that a system antimicrobial agent is necessary. That is the dilemma that I think is one that is worthy of further consideration to delineate how much benefit there is, in part with the wound score, to delineate those patients who would be appropriate recipients of this agent.

DR. GERDING: My problem with a placebo-controlled trial is using debridement as an indication because I think

there are variations in debridement. When you give somebody a pill you have given them one pill. Sure, there may be some variations in absorption but I think the amount of debridement that is done can vary markedly. I mean, I think if Dr. Miller's place was involved in it there would be very extensive debridement, while somewhere else there may not be. I think it all depends on who you enlist as to what the outcome is going to be. If you enlist a lot of people that strongly believe and are biased that debridement is going to work, it is going to be very extensive but that may not be what happens in the real world.

DR. RELLER: Everyone agrees that debridement is crucial in this process. What I was thinking about in terms of a clinical trial that all would get debridement and you would randomize them to get the vehicle or the vehicle and the active compound.

DR. GERDING: My experience when it comes to debridement is that it varies in the extent of debridement.

DR. RELLER: That is what randomization is for. I mean, I would like to have them all taken care of by Drs. Lipsky and Miller --

DR. GERDING: But I think what that would prove right away is that with very, very aggressive debridement that would happen. You would need to make sure in your trial that you had variations of debridement that are occurring

out there and not just get the most extensive ones because if you just got the ones that do the most extensive debridement, then you may be looking at a subset of what is really happening in the real world.

DR. RELLER: Are you saying that if you get extensive debridement you may not be able to show efficacy and that would deny the drug to those who would get it coupled with inadequate debridement? Where is that going to lead us?

DR. GERDING: Well, it is what is happening in the real world as to the extent of debridement. I mean, if you cut away all of the entire infection I think all of us would agree that debridement might be effective. But I am not sure that we do that, and if you are very aggressive, doing it repeatedly, following the patients very closely, I think you probably could show it but I don't think that is what happens in the real world. There are not podiatrists and people out there to see these patients that frequently to be able to do it that way, and often what happens in any clinical trial is that they oftentimes get much better care than they would normally get in their regular practice.

So, I think you could design it in such a way that it would end up giving you the answer that you want, no matter what way you want to lead.

DR. RELLER: I was just thinking that if one

doesn't have adequate debridement, then you would want to be very sure that the compound was efficacious. I mean, admittedly there are going to be varying degrees of wound care but it makes it all the more important to know what additional value this or any compound is adding to that wound care, and knowing it with a reasonable degree of certainty so that you could rank them. I mean, as Dr. O'Fallon nicely pointed out, what is a worthwhile increment of good outcome along with what should be done for everyone but may be done to varying degrees of quality?

DR. CRAIG: Okay, so we have a placebo trial. Other suggestions of things that should be done? I have already stated that I think the question on wound healing is something that needs to be addressed because, if there was some impairment there, that would nicely explain some of the differences that were observed fm the two trials. Yes, Dr. O'Fallon?

DR. O'FALLON: I want to reply to the comment that it would take as big a trial. Actually, to do a superiority trial, which this would be if it were a cream against a placebo, those can be done with fewer patients because you are generally looking for bigger differences. The problem with equivalence is that you are trying to prove that the difference is small. You can usually do it with a smaller trial.

DR. CRAIG: Except, I think, our studies within the Division for equivalence are not really true equivalence trials. They do require a smaller number than, I think, if you were trying to really prove true equivalence. I mean, we have given some set variation sizes ahead of time.

DR. CHIKAMI: Although, as you recall, this was a topic that was discussed at our advisory committee meeting in July, that in the most recent version of the draft guidances we are, in fact, sort of reassessing those sorts of statements in terms of defining what is a clinically meaningful difference that should be ruled out in a setting of an active control trial.

DR. CRAIG: Any other suggestions of things that should be done? Validation of the infection score. Some feel a placebo-controlled trial;, looking at the question of wound healing, effect on wound healing. Anything else that anyone else has to suggest?

DR. RODVOLD: In that infection score, I think people were also saying -- and you make it a little simpler than it was, do you need every piece that was currently in it so that it is maybe more user friendly and so people would use it, and can it be modified a little bit or not? I don't know. So, there are two things in there.

DR. CRAIG: Okay. Anything else?

DR. RELLER: This validation in terms of future

things, is validation of a wound score, a usable wound, a necessary ingredient to properly position ultimately this compound for who should receive it?

DR. CRAIG: Do we know in the ofloxacin study for which the drug is approved how much debridement was done in that study?

DR. CHIKAMI: I would have to go back and look at the review. So, I can't comment on that right now.

MR. BOSTWICK: One thing about it, Dr. Craig, is that those are relatively small numbers of patients. There were a number of wound ulcer patients in a larger patient population. I think one of the studies had maybe 60 diabetic wound ulcer patients total, maybe 28 in one group and 30 or 40 in the other. So, because it was figured as part of a larger group patients, I don't know exactly how strict they were in debridement and things like that.

DR. CRAIG: Okay. Dr. Gerding?

DR. GERDING: Just a comment, I think there was probably no restriction on the severity of ulceration or even osteomyelitis in that ofloxacin study, if I guess correctly, so that may be a very different population of patients treated there than what we are talking about here.

I would just comment on the wound infection scoring system. It is really a surrogate for how you try to quantitate whether the patient is getting better or not. You

know, when you are validating it, what do you validate against? Well, you validate it against all these little incremental changes that take place in each of these variables. I think it would be valuable to look back at the scoring system that has been used and look at each of the variables and see if there aren't some that aren't contributing significantly, i.e., are they always the same in the patients and don't really add anything? Otherwise, I think that scoring system is going to pretty much agree with what the investigator says is happening in terms of response or cure. If it doesn't, then it really is a bad system but everything they showed us would suggest to me that it is going to be valid, and I think it was made up because that is what we think contributes to our gestalt about how a patient is doing. So, other than eliminating useless variables, I don't see that we are going to get a whole lot more out of that wound scoring system.

DR. CRAIG: I guess the question that some people were raising was can you use a certain score to identify a subset of patients for which topical therapy would be appropriate, and certain scores for which system therapy would be required to help better define the population. At least, that is what I thought Dr. Norden was trying to bring across with trying to validate it, to use the score as a way of trying to identify which patient population might benefit

from using the topical agent.

DR. GERDING: Well, to the extent that you might be able to identify failures by a certain score --

DR. CRAIG: Right, and that is the other thing, the question where there is a certain score where they fail with treatment with topical therapy, and would that have been an important determinant in this as well.

DR. GERDING: The company should be able to tell us that from analyzing their scores, and that should be something they can achieve with their existing data.

DR. CRAIG: Yes?

DR. HOLROYD: I would just comment briefly that there certainly is a correlation between cured, improved and failed with the clinical response and the wound infection score, for example.

DR. CRAIG: So, the higher the score --

DR. HOLROYD: The more improvement in the score correlated nicely, I believe, with cured, improved and failed as clinical outcomes, but this addresses more the outcome and not a prospective use of it.

DR. LIPSKY: If I may just make one comment, there did not exist any wound infection score and we made this up.

DR. CRAIG: Sure.

DR. LIPSKY: To my knowledge, no drug that is currently approved for uncomplicated or complicated

infection has been asked to meet a standard of a certain wound score. This company, at my urging, went out on a limb to develop a score so that we could have a quantitative ability to say at the end that these patients did or did not get better. So, to say that the wound score wasn't good enough and to hold it to that standard doesn't seem, to me, exactly fair compared to the way other compounds have been looked for the same or similar indication.

DR. CRAIG: I think what the committee felt was that it was useful information, at least that is what I remember them telling us, but their only concern was that -- you are right -- this is the first time it has been used. Is it also going to prove valuable in others?

I think what I am hearing from what appears to be the majority of people, the major concern that they have in terms of the efficacy is how much this was due to the debridement as compared to how much of this was due to the topical agent. At least in my mind, that is the biggest question that the majority of the committee has as to whether there is efficacy.

As I said, for the score what Dr. Norden was primarily saying is would this score be useful for including in the package insert some way of identifying that population that would respond well to this form of therapy.

Comments or questions? Any questions from the FDA

in addition to what we have discussed already?

DR. CHIKAMI: No, we have no further questions.

DR. CRAIG: Okay, we will be adjourned. Thank you for your time and efforts.

[Whereupon, at 4:35 p.m. the proceedings were adjourned.]

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CERTIFICATE

I, **ALICE TOIGO,** the Official Court Reporter for Miller Reporting Company, Inc., hereby certify that I recorded the foregoing proceedings; that the proceedings have been reduced to typewriting by me, or under my direction and that the foregoing transcript is a correct and accurate record of the proceedings to the best of my knowledge, ability and belief.

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Lawyer's Notes