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DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

COPY

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66TH MEETING

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Holiday Inn
Kennedy Ballroom
8777 Georgia Avenue
Silver Spring, Maryland

PARTICIPANTS

William Craig, M.D., Chairperson

Kathleen Reedy, Executive Secretary

MEMBERS

Barth Reller, M.D.
Gordon Archer, M.D.
Barbara Murray, M.D.
Carl Norden, M.D.
Judy Parsonnet, M.D.
Robert Danner, M.D.
Judith O'Fallon, Ph.D.

CONSUMER REPRESENTATIVE

Keith Rodvold, Ph.D.

CONSULTANT

O. Fred Miller, M.D.

GUEST

Dale Gerding, M.D.

FDA

Li Ming Dong, Ph.D.
David Bostwick
Rosemary Roberts, M.D.
Gary Chikami, M.D.
Sandra Kweder, M.D.

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P R O C E E D I N G S

Call to Order and Introductions

1
2
3 DR. CRAIG: I would like to welcome you all to the
4 66th Anti-Infective Drugs Advisory Committee meeting. The
5 microphones are a little different today. As I understand,
6 you don't have to go ahead and pull it over, and stick the
7 mike directly in front of your mouth in order to be heard,
8 but you do have to push a button to turn it on, and a red
9 light will come on and it will also light up here. So, that
10 is the new equipment that we have.

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

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

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

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

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

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

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

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

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

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

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

19 MS. REEDY: Kathleen Reedy, FDA.

20 DR. CRAIG: Bill Craig, University of Wisconsin.

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

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

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

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

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

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

7 DR. KWEDER: I am Sandra Kweder, FDA.

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

10 **Conflict of Interest Statement**

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

15 Based on the submitted agenda for the meeting and
16 all financial interests reported by the participants, it has
17 been determined that all interest in firms regulated by the
18 Center for Drug Evaluation and Research which have been
19 reported by the participants present no potential for a
20 conflict of interest as presented at this meeting.

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

1 the record.

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

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

8 **Introductory Comments**

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

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

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

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

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

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

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

1 the problems that we face.

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

6 [Slide]

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

9 [Slide]

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

13 [Slide]

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

18 [Slide]

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

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

3 [Slide]

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

6 [Slide]

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

12 [Slide]

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

15 [Slide]

16 -- and smaller --

17 [Slide]

18 -- and smaller --

19 [Slide]

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

25 I will mention antibiotics because that is what we

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

3 [Slide]

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

8 [Slide]

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

16 [Slide]

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

20 [Slide]

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

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

3 [Slide]

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

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

16 [Slide]

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

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

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

3 [Slide]

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

12 [Slide]

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

19 [Slide]

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

1 the pressure points as much as possible.

2 [Slide]

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

9 [Slide]

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

13 [Slide]

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

16 [Slide]

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

23 [Slide]

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

1 [Slide]

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

5 [Slide]

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

8 [Slide]

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

12 [Slide]

13 It is debrided, and debrided aggressively.

14 [Slide]

15 There is the callous.

16 [Slide]

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

19 [Slide]

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

23 [Slide]

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

1 [Slide]

2 She was on systemic antibiotics.

3 [Slide]

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

6 [Slide]

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

11 [Slide]

12 This is a cluster of pieces of bony fragments.

13 [Slide]

14 Here she is after we debrided her.

15 [Slide]

16 We packed this with saline gauze.

17 [Slide]

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

20 [Slide]

21 She is healing.

22 [Slide]

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

1 debridement.

2 [Slide]

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

5 [Slide]

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

9 [Slide]

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

14 [Slide]

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

17 [Slide]

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

21 [Slide]

22 Here he is after seven weeks of contact casting.

23 [Slide]

24 This was before. This had to be aggressively
25 debrided.

1 [Slide]

2 Here it is when it is healed.

3 [Slide]

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

6 [Slide]

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

10 [Slide]

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

13 [Slide]

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

17 [Slide]

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

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

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

6 [Slide]

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

11 [Slide]

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

21 [Slide]

22 In these superficial ulcers that we are talking
23 about -- and this is from the Joselin group -- about 54
24 percent of them had Staph. aureus; Gram-negative staph in
25 42; strep in 31; Gram-negative bacilli in 23 and anaerobes

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

2 [Slide]

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

8 [Slide]

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

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

24 [Slide]

25 This was a recent case, just within the last

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

5 [Slide]

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

13 [Slide]

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

20 [Slide]

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

24 [Slide]

25 So, the conclusions here: When we face a diabetic

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

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

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

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

21 Thank you.

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

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

1 ulcers that might respond to a topical in here.

2 DR. MILLER: Yes.

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

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

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

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

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

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

25 The point that I want to make is that a person

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

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

12 DR. CRAIG: Dr. Archer?

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

15 DR. MILLER: Yes.

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

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

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

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

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

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

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

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

16 **Sponsor Presentation**

17 **Introduction and Overview**

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

19 [Slide]

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

25 [Slide]

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

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

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

19 [Slide]

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

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

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

12 [Slide]

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

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

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

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

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

15 [Slide]

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

21 [Slide]

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

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

5 [Slide]

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

8 [Slide]

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

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

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

25 We then had submitted, previous to the conclusion

1 of the impetigo study, an IND for the treatment of infected
2 diabetic foot ulcers. We initiated the first pivotal study
3 in August of 1994, and the second pivotal study in August of
4 1995. These two studies of infected diabetic foot ulcers
5 remain, to our knowledge, the largest studies of
6 antimicrobial therapy for this condition ever conducted.

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

10 [Slide]

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

15 [Slide]

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

19 **Diabetic Foot Ulcers and Medical Need**

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

25 [Slide]

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

7 [Slide]

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

15 [Slide]

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

24 [Slide]

25 In the twenty minutes allotted to me, I would like

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

6 [Slide]

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

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

1 occur in the United States every year.

2 [Slide]

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

13 [Slide]

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

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

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

4 [Slide]

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

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

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

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

6 [Slide]

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

17 [Slide]

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

1 [Slide]

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

10 [Slide]

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

16 [Slide]

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

25 [Slide]

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

11 [Slide]

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

22 [Slide]

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

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

13 [Slide]

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

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

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

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

11 [Slide]

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

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

22 [Slide]

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

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

6 [Slide]

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

16 [Slide]

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

21 [Slide]

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

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

5 [Slide]

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

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

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

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

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

13 [Slide]

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

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

25 [Slide]

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

12 [Slide]

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

21 [Slide]

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

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

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

14 [Slide]

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

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

1 infections.

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

5 [Slide]

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

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

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

20 [Slide]

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

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

9 [Slide]

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

17 [Slide]

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

25 There is at present only one antibiotic agent that

1 is specifically approved for the treatment of diabetic foot
2 infections, as previously mentioned, and that is
3 trovafloxacin.

4 [Slide]

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

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

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

23 [Slide]

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

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

8 [Slide]

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

16 Thank you very much.

17 **Preclinical Background, Microbiology, Clinical Studies**

18 [Slide]

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

24 [Slide]

25 Regarding the preclinical background, we will look

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

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

12 [Slide]

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

22 [Slide]

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

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

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

15 [Slide]

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

24 [Slide]

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

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

11 [Slide]

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

18 [Slide]

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

1 crustaceans, birds and mammals up through man.

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

14 [Slide]

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

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

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

4 [Slide]

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

14 [Slide]

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

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

1 [Slide]

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

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

22 [Slide]

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

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

10 [Slide]

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

1 [Slide]

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

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

12 [Slide]

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

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

3 [Slide]

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

14 [Slide]

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

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

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

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

13 [Slide]

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

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

2 [Slide]

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

13 [Slide]

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

19 [Slide]

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

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

4 [Slide]

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

11 [Slide]

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

18 [Slide]

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

1 concentration.

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

6 [Slide]

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

13 [Slide]

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

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

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

6 [Slide]

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

11 [Slide]

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

15 [Slide]

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

24 [Slide]

25 Coagulase-negative staphylococci in our patients,

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

5 [Slide]

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

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

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

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

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

15 [Slide]

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

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

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

5 [Slide]

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

15 [Slide]

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

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

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

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

20 [Slide]

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

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

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

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

21 [Slide]

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

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

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

9 [Slide]

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

13 [Slide]

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

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

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

3 [Slide]

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

19 [Slide]

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

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

8 [Slide]

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

19 [Slide]

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

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

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

5 [Slide]

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

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

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

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

9 [Slide]

10 As I mentioned a moment ago, this outlines for our
11 two studies, which we called study 303 and the second study
12 304, the percentage of patients which underwent debridement
13 by visits during the study. We can see here the visit and
14 the percentage which underwent debridement for the two
15 treatment groups.

16 We can see that at the baseline visit about 94
17 percent of patients entering the study underwent
18 debridement. By the end of the study there was still about
19 60 percent of patients who were undergoing debridement at
20 their follow-up visit, which was two weeks after the end of
21 treatment, in order to clean any debris from the ulcers.

22 [Slide]

23 In our two studies -- again, study MSI-79-303
24 which we refer to as study 303, and the second study, the
25 304 study, we enrolled in total 835 patients for the

1 comparison of pexiganan cream one percent to ofloxacin.

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

15 [Slide]

16 The time points for our therapy and the
17 assessments are outlined here. Patients received therapy for
18 14 to 28 days at the discretion of the investigator.
19 Essentially, if the investigator felt that the ulcer
20 infection was cured after 14 days therapy could be stopped
21 at that visit. If they felt that the patient was not cured
22 at that visit and wished to continue on with the
23 antimicrobial therapy, it could be conducted out to 28 days.

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

1 visit followed by assessments at which data was collected at
2 days 3, 10 and 14 and day 21 if therapy had not already been
3 stopped. But recall that in many data analyses you will see
4 the end of treatment visit and that, again, varied from 14
5 to 28 days and finally the follow-up visit which took place
6 2 weeks after the end of treatment visit.

7 So, in summary, these patients in general received
8 2-4 weeks of therapy and they were seen, depending on the
9 length of therapy, 4 to 6 weeks afterwards.

10 [Slide]

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

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

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

25 [Slide]

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

7 [Slide]

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

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

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

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

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

11 [Slide]

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

17 [Slide]

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

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

2 [Slide]

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

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

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

25 What we did further, after the study was

1 concluded, was to look at how many of the patients, with the
2 best information we had, that had this history of amputation
3 and foot surgery had actually a history of amputation. This
4 was also reported on the case report form by the specific
5 surgical procedure that had been performed previously. We
6 see that in particular there was an excess of this
7 amputation history in the pexiganan patients in study 303
8 compared to the ofloxacin patients in 303 or compared to the
9 history of amputation among either treatment group in the
10 304 study.

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

14 [Slide]

15 Let's look now at the efficacy data.

16 [Slide]

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

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

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

16 [Slide]

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

25 We would agree that consistently and in the

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

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

13 [Slide]

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

19 [Slide]

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

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

3 [Slide]

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

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

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

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

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

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

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

24 [Slide]

25 Just to spend one more moment on these two per-

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

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

23 [Slide]

24 Let's look now at the data.

25 [Slide]

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

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

17 [Slide]

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

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

7 We see here that at day 10 there was 84 percent
8 response in study 303 for pexiganan and 89 percent in study
9 304. For ofloxacin the range in the two studies is 88-90
10 percent. The confidence interval limits are shown here. They
11 all cross zero, meaning that the p value is greater than
12 0.05, and they are all within 15 percent of the lower bound
13 of the confidence limit.

14 [Slide]

15 Let's look now at end of treatment after 2-4 weeks
16 of treatment. We see that for study 303 and here for the
17 intent-to-treat for per-protocol 2 populations for study
18 304, the percentage of individuals who had clinical
19 response. We see that in study 303 in the two populations
20 pexiganan had an 85 percent response rate and ofloxacin a 91
21 percent response rate. We see that the 95 percent confidence
22 interval, the difference, does not cross zero for the
23 intent-to-treat population. At end of treatment in the per-
24 protocol 2 population it does cross zero and the lower bound
25 is within 15 percent.

1 In study 304 we have pexiganan response rates of
2 89 and 91 percent, and similar for ofloxacin, with
3 confidence intervals evenly straddling zero.

4 [Slide]

5 Let's look now at the follow-up visit. We see here
6 that in study 303 pexiganan's clinical response rate is 75-
7 77 percent. For ofloxacin it is 84 percent for the two
8 populations. The 95 percent confidence interval does not
9 cross zero; it is within 15 percent. In the per-protocol 2
10 group it does slightly cross zero and is beyond the 15
11 percent limit for the confidence interval on the down side.

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

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

20 [Slide]

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

1 these 6 populations.

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

8 [Slide]

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

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

1 but, of course, that remains speculative.

2 [Slide]

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

10 [Slide]

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

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

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

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

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

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

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

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

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

18 [Slide]

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

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

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

7 [Slide]

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

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

1 [Slide]

2 In 304 there is a similar phenomenon where about
3 40 percent of the patients, slightly higher in the ofloxacin
4 treatment group in the follow-up visit, had infection
5 resolved, again, the most common category.

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

9 [Slide]

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

21 [Slide]

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

1 treatment was 48-53 percent for pexiganan, 47-48 percent for
2 ofloxacin. The confidence intervals well straddle zero. In
3 study 304 we had a similar finding for overall
4 microbiological outcome at end of treatment, with pexiganan
5 46-51 percent and ofloxacin 47-52 percent. Again, the
6 confidence intervals well straddle zero.

7 [Slide]

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

19 [Slide]

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

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

9 [Slide]

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

22 [Slide]

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

1 clinical response for both treatments in the studies at day
2 10, at the end of treatment where it was 85-91 percent for
3 pexiganan and 89-91 percent for ofloxacin in the data that I
4 showed you, and at follow-up 75-83 percent for pexiganan and
5 84-86 percent for ofloxacin.

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

11 [Slide]

12 In terms of these efficacy data for clinical,
13 microbiological outcome and therapeutic response, for study
14 303 I would summarize that we showed you that pexiganan
15 cream was equivalent to ofloxacin for subject
16 microbiological outcome and for therapeutic response. For
17 clinical outcome, particularly at the follow-up visit, we
18 did not stay within, either crossing zero or in the case of
19 the other population going below 15 percent for the 95
20 percent difference in the confidence interval.

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

25 [Slide]

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

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

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

1 history of osteomyelitis.

2 [Slide]

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

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

23 [Slide]

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

1 assessment and baseline pathogen eradication.

2 [Slide]

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

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

18 [Slide]

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

25 In addition to this wound infection score, we made

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

8 [Slide]

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

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

20 [Slide]

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

1 [Slide]

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

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

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

16 [Slide]

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

22 [Slide]

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

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

7 [Slide]

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

13 [Slide]

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

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

1 following way, the central values, or the mean, or 50th
2 percentile of improvement. The upper bars are the 25th
3 percentile of improvement and the lower bars are the 75th
4 percentile of improvement for pexiganan and ofloxacin in the
5 303 study. We can see that these look very similar.

6 [Slide]

7 Let's look now at the 304 study. We see here that
8 in the 304 study for the median change in wound area over
9 time there is a slight increase in the improvement in wound
10 area for ofloxacin compared to pexiganan, which for the
11 median change is about minus 60 mm² improvement for
12 pexiganan and about 90 mm² improvement for ofloxacin at the
13 follow-up visit. You can see also that ofloxacin is favored
14 for improvement in this median wound area for the 25th and
15 75th percentile of improvement. Again the improvements are
16 in the order or about 30 mm² greater.

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

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

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

10 [Slide]

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

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

25 In general, the mean percentage of reduction in

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

6 [Slide]

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

22 [Slide]

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

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

2 [Slide]

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

8 [Slide]

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

11 [Slide]

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

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

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

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

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

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

7 [Slide]

8 So, we see here that for total pathogens present
9 at baseline and eradicated at follow-up, it was 66 percent
10 and 69 percent for pexiganan and ofloxacin, 62 percent and
11 66 percent for all pathogens in the studies.

12 [Slide]

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

20 [Slide]

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

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

3 [Slide]

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

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

24 [Slide]

25 We see this similar phenomenon occurring if we

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

5 [Slide]

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

17 [Slide]

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

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

4 [Slide]

5 Let's look now at the safety data.

6 [Slide]

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

10 [Slide]

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

16 We have done three studies looking at the so-
17 called maximization protocol which we believe assesses
18 sensitization potential. We have shown that there is minimal
19 to mild skin sensitization potential for pexiganan in these
20 studies. In the largest of the studies, which included over
21 200 subjects, the investigator's conclusion was that there
22 was no evidence of skin sensitization for pexiganan.
23 However, there was a slight increase in the number of local
24 increases of erythema at the patch site. I could talk more
25 about this in a moment but will say that in these skin

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

10 [Slide]

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

15 [Slide]

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

21 [Slide]

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

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

8 [Slide]

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

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

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

1 the indulgence. I appreciate it.

2 [Slide]

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

5 [Slide]

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

10 [Slide]

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

15 [Slide]

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

20 [Slide]

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

1 [Slide]

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

6 [Slide]

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

11 [Slide]

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

17 [Slide]

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

22 [Slide]

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

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

7 [Slide]

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

13 [Slide]

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

21 [Slide]

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

1 outpatients.

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

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

17 [Slide]

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

24 [Slide]

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

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

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

11 [Brief recess]

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

14 **FDA Clinical and Statistical Presentation**

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

17 [Slide]

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

1 [Slide]

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

7 [Slide]

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

10 [Slide]

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

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

21 [Slide]

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

1 [Slide]

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

10 [Slide]

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

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

24 [Slide]

25 There were 493 patients randomized to study 303.

1 As was earlier mentioned, there was also a two percent
2 formulation utilized in the original study design. There was
3 a planned interim analysis to see how the two percent and
4 the one percent were doing against one another. There was no
5 significant difference noted between the one percent and two
6 percent formulations so the two percent formulation was
7 dropped, and no statistical adjustment was made for this
8 procedure. I should mention that the 493 patients here are
9 only one percent pexiganan and ofloxacin patients. In study
10 304 there were 342 patients randomized. It was only one
11 percent pexiganan versus ofloxacin.

12 [Slide]

13 A little bit about the inclusion criteria -- the
14 patients were to have active diabetes. They were not
15 required to be insulin dependent. They were to have a full
16 or partial thickness foot ulcer at least 0.5 cm² in area.
17 They must have been able to be treated on an outpatient
18 basis, which means for our purposes that the patients
19 applied their own medications after instruction by the
20 investigator and, as you have seen, the study targeted
21 patients with localized infection who had no systemic signs
22 of infection at study entrance.

23 [Slide]

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

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

5 [Slide]

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

13 [Slide]

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

18 [Slide]

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

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

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

9 [Slide]

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

19 [Slide]

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

1 the ofloxacin group.

2 [Slide]

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

10 [Slide]

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

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

21 [Slide]

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

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

12 [Slide]

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

20 [Slide]

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

1 moment.

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

6 [Slide]

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

13 [Slide]

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

21 [Slide]

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

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

12 [Slide]

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

22 [Slide]

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

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

7 [Slide]

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

14 [Slide]

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

20 [Slide]

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

1 group in study 304 than in the ofloxacin group.

2 [Slide]

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

8 [Slide]

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

14 [Slide]

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

21 [Slide]

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

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

3 [Slide]

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

13 [Slide]

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

19 [Slide]

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

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

3 [Slide]

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

10 [Slide]

11 As far as mean wound size goes, there does appear
12 to have been a difference. Ofloxacin in this study had been
13 better in reducing the wound size, 149 mm² to 90 mm², which
14 has a p value of 0.08, and in per-protocol the difference
15 was 132 mm² versus 79 mm², which has a p value of 0.035.

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

19 [Slide]

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

25 [Slide]

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

9 [Slide]

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

18 [Slide]

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

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

3 [Slide]

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

8 [Slide]

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

21 [Slide]

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

24 [Slide]

25 There are a few reasons why we are particularly

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

7 [Slide]

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

15 [Slide]

16 This slide shows median wound size by study visits
17 for study 303. The solid red line stands for the pexiganan
18 group; the blue broken line represents the ofloxacin group.
19 Both pexiganan and ofloxacin groups demonstrated wound size
20 reduction over time. Wound size of both treatment groups
21 started with 125 mm² and by the follow-up visits both were
22 below 50 mm².

23 [Slide]

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

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

4 [Slide]

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

11 [Slide]

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

16 [Slide]

17 Since wound size reduction measures wound healing,
18 here is a graph which shows the distribution of changes in
19 wound size at follow-up. The blue bars are for the pexiganan
20 group, and the transparent bars are for the ofloxacin
21 patients. The horizontal scale for each bar is 50 mm². We
22 observed a wide range of changes in wound size for both
23 treatment groups. Most of the values fell below zero, which
24 means that most of the patients had wound size reduced, but
25 not all of them.

1 [Slide]

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

10 [Slide]

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

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

1 average ofloxacin patients had about 103 mm² more reduction
2 in wound size than the pexiganan-treated patients. If we
3 look at the per-protocol patients, the ofloxacin group had
4 36 mm² more reduction than the pexiganan group.

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

12 [Slide]

13 This table is a similar table to the previous one
14 but for 304. In this study, ofloxacin-treated patients
15 showed a larger wound size reduction, no matter which
16 population, no matter whether measured by mean or median.
17 The average reduction for ofloxacin is 59 mm², more than
18 that of pexiganan-treated patients, with a p value of 0.008
19 in the ITT population.

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

25 [Slide]

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

9 This table shows that even after adjusting for
10 baseline wound size the ofloxacin group still had a larger
11 reduction in wound size. For study 303 ITT population on
12 average the wound size in the ofloxacin arm was reduced 27
13 mm² more than that of the pexiganan patients with the same
14 baseline wound size. That is, if the two treatment arms
15 started with the same wound size at baseline, at follow-up
16 the wound size of the ofloxacin group would be 27 mm²
17 smaller than that of the pexiganan group.

18 Other values can be interpreted the same way. For
19 the per-protocol population in the same study the adjusted
20 difference between the two treatments is 53 mm², with a p
21 value of 0.009. Results of study 304 remained similar with
22 or without baseline adjustments, no matter which population
23 we are looking at. All p values for study 304 suggested that
24 the differences between the treatment groups in wound size
25 reduction were statistically significant favoring ofloxacin.

1 [Slide]

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

14 [Slide]

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

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

1 missing values were dropped the results also remained
2 qualitatively similar.

3 [Slide]

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

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

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

16 MR. BOSTWICK: There are a few more slides.

17 [Slide]

18 I am briefly going to go over the safety. We have
19 obviously not listed all the adverse events seen, but simply
20 the most frequent or the most remarkable. You can see that
21 42 percent of the pexiganan patients versus 46 percent of
22 the ofloxacin patients reported at least one adverse event.
23 The numbers are reasonable comparable. There are a few more
24 cellulitis patients in the pexiganan group. Obviously for
25 insomnia there was a greater predominance of patients in the

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

3 [Slide]

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

13 [Slide]

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

21 [Slide]

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

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

5 [Slide]

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

10 [Slide]

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

20 [Slide]

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

1 ruling out a 15 percent difference between the test
2 articles.

3 [Slide]

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

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

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

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

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

3 MR. BOSTWICK: I think we got that number from the
4 guidance for skin and skin structure studies. Well, that
5 number is really 50 percent for microbiology patients. Where
6 we got the 50 percent was we looked at some references that
7 the Magainin people were kind enough to send to us, and we
8 also looked at the ofloxacin results. Now, those are
9 probably more seriously ill patients, but we found about a
10 50 percent cure rate amongst the Trovan patients. So, we
11 took that to be an acceptable number, although we don't have
12 a real basis for it outside our sense of it.

13 DR. CRAIG: Dr. Norden?

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

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

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

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

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

17 MR. BOSTWICK: Right.

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

19 MR. BOSTWICK: Right.

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

24 MR. BOSTWICK: It should have been.

25 DR. CRAIG: Even though it might not have been

1 recovered on a subsequent culture?

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

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

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

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

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

3 DR. CRAIG: Dr. Gerding?

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

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

12 DR. CRAIG: Yes, Dr. Roberts?

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

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

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

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

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

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

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

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

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

23 DR. HOLROYD: Yes, sir.

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

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

1 after lunch, Dr. Craig.

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

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

18 DR. CRAIG: Dr. Gerding?

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

25 DR. DONG: We included all the patients.

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

3 DR. DONG: Right.

4 DR. CRAIG: Dr. Parsonnet?

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

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

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

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

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

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

7 DR. PARSONNET: Yes, if you did medians.

8 DR. DONG: We didn't do medians.

9 DR. CRAIG: Yes, Dr. Miller?

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

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

25 There is an explanation of them in the FDA review

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

7 DR. CRAIG: Dr. Parsonnet?

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

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

1 score. They were slightly different but not terribly
2 different. In terms of patients who were actually infected,
3 I don't know, I think we only left out something like 13 or
4 14 percent of the patients with low wound infection scores.
5 If you can accept that symptomatology, the erythema and
6 things like that, and purulence obviously, as signs of
7 infection, then I think we probably had about 85 percent of
8 the patients in the study we were pretty sure were infected.

9 DR. CRAIG: Dr. Murray?

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

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

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

20 DR. CRAIG: Maybe after lunch?

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

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

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

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

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

19 DR. CRAIG: Dr. Gerding?

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

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

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

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

12 DR. CRAIG: Yes, Dr. Rodvold?

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

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

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

4 DR. CRAIG: Yes?

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

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

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

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

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

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

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

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

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

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

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

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

12 MR. BOSTWICK: The only one I know is Trovan,
13 trovafloxacin.

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

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

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

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

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

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

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

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

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

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

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

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

19 DR. CRAIG: Dr. Norden?

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

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

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

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

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

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

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

1 in this current pexiganan study.

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

7 **Open Public Hearing**

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

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

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

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

3 Diabetic foot ulcers, as well as other foot
4 problems are a major burden for both the individual and the
5 healthcare system and may increase as the population ages.
6 Fifteen percent of all patients with diabetes will develop
7 foot ulcers during their lifetime, and 20 percent of these
8 ulcerations will lead to amputations. In fact, 86 percent of
9 lower extremity amputations were preceded by diabetic foot
10 ulcers. More than half of all lower limb amputations in the
11 United States occur among people with diabetes. From 1993-
12 1995, about 67,000 amputations were performed each year
13 among people with diabetes. After amputation, the chance of
14 another amputation of the same extremity or of the opposite
15 extremity within 5 years is as high as 50 percent. The 5-
16 year mortality rate after lower extremity amputation ranges
17 from 39 to 69 percent.

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

25 The American Podiatric Medical Association

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

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

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

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

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

5 DR. HOLROYD: Fine.

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

10 DR. HOLROYD: Thank you.

11 DR. CRAIG: Any others?

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

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

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

1 AFTERNOON PROCEEDINGS

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

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

8 [Slide]

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

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

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

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

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

17 You will note that in the 303 study ofloxacin had
18 very similar point estimate rates of the clinical response
19 whether this history was present or not. In contrast, in the
20 304 study you will note that pexiganan for these patients in
21 this study, with this history of amputation, had little
22 difference in clinical outcome, 4 percent positive, 5
23 percent negative, between end of treatment and follow-up,
24 and ofloxacin had a point estimate 8 percent lower and 10
25 percent lower for patients with this history of

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

3 [Slide]

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

9 [Slide]

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

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

23 [Slide]

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

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

7 We see here that at the end of treatment men
8 compared to women tended to have a slightly lower point
9 estimate of the response and at follow-up, however, in the
10 303 study this really was not evident.

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

16 I think what we can say for this history of
17 osteomyelitis and amputation, in a simple-minded way from
18 these type of analyses, that there are many things
19 contributing to clinical response. Among the patients in the
20 303 study with this history pexiganan tended to have a lower
21 clinical response for people with this history of
22 amputation, and in the 304 study ofloxacin tended to have a
23 lower response for people with this history. The imbalance
24 was for the people with the history in the 303 study.

25 [Slide]

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

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

16 [Slide]

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

25 [Slide]

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

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

16 [Slide]

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

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

25 Models containing treatment with the above showed

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

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

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

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

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

1 some ranges in my talk presentation from this morning.

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

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

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

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

5 DR. ARCHER: Thank you.

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

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

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

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

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

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

19 DR. CRAIG: Yes, Dr. Danner?

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

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

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

11 DR. CRAIG: Dr. Miller?

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

15 DR. HOLROYD: It was Enterococcus.

16 DR. MILLER: Enterococcus.

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

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

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

2 [Slide]

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

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

15 [Slide]

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

23 [Slide]

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

1 surface of the skin, incubate and sample.

2 [Slide]

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

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

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

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

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

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

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

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

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

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

18 [Slide]

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

7 DR. CRAIG: Other questions? Dr. Murray?

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

22 DR. CRAIG: Dr. Parsonnet?

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

1 results.

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

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

11 We did look statistically -- I am not an expert at
12 all on these results, for an outcome by center that you
13 referred to. As we showed, there were about 80 centers that
14 participated in the study. Some of them had low enrollment,
15 and these were defined in the so-called pseudo-centers for
16 this treatment by center analysis. I think the p value -- I
17 can't remember, was supposed to be either 0.10 or 0.15 to
18 show a significant interaction and it wasn't found. It was
19 0.15, Mr. Height tells me.

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

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

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

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

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

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

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

7 DR. HOLROYD: I believe that Mr. Bostwick from FDA
8 or the statistical reviewer from the Division showed some of
9 that data. Just to give an overall summary, it was about 20
10 percent of the patients in the studies. We also showed some
11 data on percentage improvement and, again, as a rough
12 figure, 50 percent of the people were cured clinically. The
13 50 percent that had the clinical response of cured, their
14 mean or median percentage improvement in the ulcer was in
15 the range of 70-90 percent. So a lot of these had closed a
16 significant amount among those people.

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

1 20 percent of people; and there was no culture taken, and we
2 consider those infections resolved. From the rest of the
3 people, from what we can tell for at least the majority,
4 overall among this 40 percent of people, did not have a
5 culture result in their infection resolved, but I don't have
6 an exact figure for you.

7 DR. CRAIG: Okay. Dr. Archer?

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

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

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

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

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

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

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

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

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

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

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

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

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

1 all on as a solution into the wound.

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

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

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

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

19 DR. HOLROYD: Yes.

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

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

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

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

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

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

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

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

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

11 DR. HOLROYD: Yes, I believe so.

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

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

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

25 DR. MURRAY: And that was physician driven, based

1 on their gestalt at the time?

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

4 [Slide]

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

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

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

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

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

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

7 [Slide]

8 This is information that the applicants provided
9 to us earlier in the week, and these are basically tables
10 provided from line listings. These are clinical failures at
11 follow-up for the intent-to-treat population for both study
12 303 and 304.

13 In the upper panel, for pexiganan there was a
14 total of 58 failures. Of those, 13, or 22 percent, required
15 an infection-related hospitalization; 3, or 5 percent, had
16 an amputation during the study follow-up period. For
17 ofloxacin there was a total of 39 failures. Nine, or 33
18 percent, had an infection-related hospitalization and 5, or
19 13 percent, had an amputation.

20 For study 304, in the pexiganan arm there were 30
21 failures; 4, or 13 percent, had an infection-related
22 hospitalization; 4, or 13 percent, had an amputation. For
23 the ofloxacin arm, there were 26 failures. Seven, or 27
24 percent, had a hospitalization; and 3, or 12 percent, had an
25 amputation.

1 DR. CRAIG: Thank you, Dr. Chikami. Any other
2 comments that you wanted to make? No?

3 **Committee Discussion**

4 [Slide]

5 DR. CHIKAMI: What we have is an overhead of the
6 questions that we would like to discuss. I think in general
7 many of the issues that the Division sort of has been
8 considering have been touched upon in your questions and
9 discussion after the presentation and early this afternoon,
10 after lunch.

11 I think the issues that you briefly talked about
12 are the patient population that was studied in these trials;
13 what is the sort of role of antimicrobial therapy in these
14 patients; and, more specifically, what is the potential role
15 for a topical agent in these patients; and how would one
16 appropriate define the patient population for which a
17 topical agent might be appropriate.

18 Then the other issues that have been touched upon
19 are sort of the overall assessment of the clinical data, not
20 only the clinical response but other endpoints that have
21 been discussed -- not only the measurement of wound scores
22 and the change in size of the wound, how relevant is that to
23 your overall assessment, and also, as was importantly
24 pointed out or discussed, the microbiologic assessments --
25 what do those tell you about the effectiveness or the

1 utility of such a product in the overall treatment of
2 infected diabetic foot ulcers.

3 So, I will just briefly review the questions and
4 then stop there. The first question is discuss your
5 assessment of the data presented regarding the safety and
6 effectiveness of pexiganan acetate for the treatment of
7 infected diabetic ulcers. Please address the following:

8 In addition to the overall clinical response,
9 which of the secondary parameters do you feel are important
10 to the evaluation of its effectiveness?

11 Part (b), please address the potential risks and
12 benefits of pexiganan acetate's clinical use for the
13 proposed indication in the population studied.

14 The second question is based on the discussion of
15 the above, do the data support the safety and efficacy of
16 pexiganan acetate?

17 If yes, in what patient population should the drug
18 be used?

19 If no, what studies would you recommend that the
20 applicant conduct to provide further evidence of safety and
21 effectiveness?

22 DR. CRAIG: Thank you. Just for everybody, if they
23 have Dr. Bostwick's presentation, I think on the third page
24 of that, slide number 13, there are listed the various
25 secondary efficacy parameters. We can make sure that we

1 touch every one of those in making our assessment. But,
2 clearly, the question is in addition to the overall clinical
3 response, which of the secondary parameters do you feel are
4 important to the evaluation of its effectiveness? The first
5 one that is listed there is microbiologic response. Comments
6 from people as to microbiologic response? Dr. Norden is
7 ready to respond.

8 DR. NORDEN: I think that I have never liked it as
9 a part of most of the studies, partly because of the issue
10 that we weren't able to get a clear answer to, which is
11 whether it is tied to the clinical response, which it often
12 is, and nobody gets a culture, and so we say the organism is
13 eradicated. I am not sure that it is terribly helpful to me
14 here.

15 The second point is we know there are lots -- not
16 lots, there are clinical situations, certainly, where the
17 organisms persists and the patient does fine. And, with
18 Klebsiella pneumoniae you can recover the organism for days
19 after the patient is improving and the patient is not a
20 failure. So I am not convinced that microbiologic response
21 is terribly helpful, and here distinguishing between
22 infection and colonization I think is very difficult.

23 DR. CRAIG: Dr. Murray?

24 DR. MURRAY: Yes, I agree. I think it is something
25 that I am interested in seeing in the context of is the

1 organism that was originally there still there and now
2 resistant, in which case you would need to do strain typing
3 to make sure it was the same organism and not a new
4 colonizer. So, in that context I would be interested,
5 particularly if it was appropriate for a drug known to have
6 mutational resistance.

7 DR. CRAIG: Yes, Dr. Archer?

8 DR. ARCHER: I just want to second and third those
9 comments, and the fact that there are a lot organisms that
10 are called to be part of the flora of an infected diabetic
11 foot that are not covered any of the drugs that are used --
12 and we could name a whole raft of them, yet they do fine.
13 So, I don't know that there is any correlation between the
14 microbiological culture result and clinical response. So, I
15 was also not terribly impressed with this. I agree.

16 My problem also is that frequently we don't do any
17 quantitative cultures so that with the skin, that is an area
18 where we have even had an advisory committee meeting on that
19 before, and just recovering the organism doesn't tell me
20 that the organism hasn't been significantly reduced in
21 numbers, which, in my mind, would be a more positive aspect.
22 So, you might see it reduced in numbers but if you are just
23 looking at whether it is there at the beginning and there at
24 the end, you might not see a difference.

25 DR. CRAIG: Yes, Dr. Rodvold?

1 DR. RODVOLD: My other concern, and I agree with
2 everything, is that it leads you to want to put it in the
3 label, and you are going to have a listing in the label that
4 will have all these organisms that were recovered and I
5 think it gives people false security potentially. So, I
6 agree with the other statements but it also leads to
7 labeling issues that I wouldn't want to see.

8 DR. CRAIG: Although here if it was included, that
9 false security might be the opposite effect since it looked
10 like there was a little less elimination with this compound
11 compared to the comparative agent. Any other comments on
12 that?

13 [No response.]

14 So, am I seeing the group sort of saying
15 microbiologic response isn't very important? Do you agree,
16 our new member from Duke, Dr. Reller?

17 DR. RELLER: This is another situation where many
18 are colonized; few are infected after adequate debridement.
19 And, the only endpoint I am interested in is an intact skin
20 covering the previous ulcer.

21 DR. CRAIG: Okay. Let's move on to the next. If we
22 don't think microbiologic is very useful, any bit push for
23 combined microbiologic and clinical since, as everybody
24 said, that is driven more by the microbiologic than by the
25 clinical response?

1 [No response.]

2 How about wound size and depth? Specifically what
3 you were looking at there was change in wound size and depth
4 over time. Dr. Murray?

5 DR. MURRAY: I think that is kind of the endpoint
6 that you are really interested in as an overall sense. I
7 think it would also be important when a topical was involved
8 to make sure, as you alluded to earlier, that it doesn't
9 delay the process as well as potentially enhancing it with
10 its antimicrobial activity.

11 DR. CRAIG: I see some head shakes. Do our
12 consultants have any comments that they want to make? Dr.
13 Miller?

14 DR. MILLER: I think certainly that wound size and
15 depth should change. But if you look at the studies that we
16 saw today, you know, there was no change, or very little
17 change after the period of time but there was no consistent
18 off-loading in these patients, and there was no
19 specification as to where those wounds were on the foot. So,
20 if you have a wound on the dorsal foot or the dorsal toe,
21 they are easy to heal. But if you have one over the first
22 metatarsal plantar head or over the heel or over the fifth
23 metatarsal head, they are difficult because you must off-
24 load those and they are the ones that are going to have the
25 exuberant callus with pressure and friction. So, some of

1 them are very, very easy to treat and others you treat with
2 difficulty. So, you must have these adjunctive measures
3 going on as you treat with either a systemic or a topical
4 antibiotic.

5 DR. CRAIG: Do we have any information on that?
6 Was there any difference between the groups in that regard?

7 DR. HOLROYD: I don't believe so. We have a
8 breakdown, Dr. Craig and Dr. Miller, where I can tell you
9 that the most common group -- we divided it into four
10 groups, plantar forefoot; plantar hind foot; dorsal lateral,
11 on the top of the foot; or toes. The most common was plantar
12 forefoot. I can show one piece of information here.

13 [Slide]

14 The second most common was toe ulcers, and then
15 dorsum and hind foot ulcers were about equally shown. So,
16 you see here broken down by these locations the clinical
17 response. This is in the 303 study. Some experts tell me, I
18 don't know if Dr. Miller would agree -- I think there is a
19 slight trend for both treatments -- again, this is the 303
20 study -- for the hind foot having a slightly lower clinical
21 response rate, and the dorsal lateral, the top of the foot
22 ulcers, at least at end of treatment, having a higher one.
23 Again, the numbers are small and the largest groups are the
24 forefoot and the toes.

25 [Slide]

1 This is the breakdown for 304 among the different
2 ulcer location types. I agree that for infected ulcers --
3 and I am certainly not an expert in off-loading techniques
4 by any means, it remains a challenge during the infection
5 period and afterwards as well.

6 DR. ARCHER: Am I to understand that the study
7 design was such that in any one patient, if they had
8 multiple ulcers that were eligible only one was treated? In
9 other words, if they had three ulcers on the foot, one was
10 chosen for treatment or all three?

11 DR. HOLROYD: Yes, Dr. Archer, the largest ulcer
12 was chosen for the treatment ulcer to be followed during the
13 study and the other ulcers, if they were considered to be
14 infected by the investigator, were also to receive either
15 the placebo cream -- whichever cream. I don't know if we
16 have a whole lot of information on what happened to these
17 secondary ulcers. I know it wasn't specifically captured.

18 DR. ARCHER: So, there is no data on comparison of
19 the same patient on the same foot of a treated versus an
20 untreated ulcer?

21 DR. HOLROYD: No. That is an interesting question.

22 DR. ROBERTS: All the ulcers that the patient had
23 were treated with whatever cream they were randomized to.
24 But, no, we don't have any data.

25 DR. CRAIG: So, I have heard so far from people

1 thinking that the changes in wound size and depth are
2 important, with the caveat, as Dr. Miller talked about, that
3 it is very dependent on where the ulcer is located as to how
4 much healing one would expect. Dr. Gerding?

5 DR. GERDING: Bill, I think ultimately the goal is
6 to try to heal these ulcers, and I realize that an
7 antimicrobial is not exactly correlated with the healing of
8 the ulcer but, rather, with treatment of infection. But I
9 still fail to understand a systematic reason why there isn't
10 as much wound healing in the topical group as there is in
11 the ofloxacin group, and I am still bothered by that
12 although I realize that that is not what the goal of an
13 antimicrobial therapy is.

14 I still don't quite understand what the difference
15 is. Maybe there is a difference because of this group that
16 is failing, perhaps having enlargement of their ulcers or
17 that group causing most of the difference in the amount of
18 wound healing that is taking place. But you would also have
19 to explain then why did those failures have more worsening
20 than the worsening that occurs with someone on a systemic
21 drug. So, I am still bothered by that. I mean, overall, I
22 really think it is remarkable that a topical agent can do as
23 well as this one has versus a systemic antimicrobial, but I
24 would like to know, and I doubt we are going to find the
25 answer today, why there is that difference in wound healing.

1 DR. CRAIG: Any other comments? Dr. Miller?

2 DR. MILLER: If I can get the data again on the
3 breakdown of the location of the ulcers in those two groups,
4 you know, were the dorsal skewed to the ofloxacin and did
5 the topical get all the real ulcers on the plantar surface,
6 or something?

7 DR. O'FALLON: Also the sizes. I mean, there is a
8 discrepancy in the sizes.

9 DR. CRAIG: The question he is asking you is you
10 gave us the numbers up there in terms of the ulcers but you
11 didn't match up size with the ulcer. I mean, were the ulcers
12 in certain positions larger than others?

13 DR. HOLROYD: I will make three very brief
14 comments. First, why we showed by ulcer location, we showed
15 by baseline wound area but I believe the clinical responses
16 by the quartiles was similar. I don't have any data to
17 answer the question if by location there was a difference in
18 the mean or median wound sizes. I don't know if Dr. Lipsky
19 has any comments on differences in sizes depending on the
20 location in his clinical experience.

21 DR. LIPSKY: I think it is highly variable and I
22 can't speak to it directly. In reference to Dr. Gerding's
23 question, I would make one other point, which is that in
24 addition to the fact that the outcome of the percentage
25 reduction in wound size depended to some degree on whether

1 one looked at mean or median, and so on, bear in mind that
2 we are also debriding these ulcers as we go along. So, an
3 ulcer can remarkably increase in size, as you saw from the
4 slides that Dr. Miller showed, between when the patient
5 walked in the door, say, on his third visit and when he
6 walked out. So, it is just a very highly variable number,
7 with a huge standard deviation around it.

8 DR. CRAIG: But in terms of complete healing, if I
9 remember right, the FDA did show that there was a difference
10 between the two compounds, or not?

11 DR. DONG: Yes, there is a difference.

12 DR. CRAIG: Which page was that on?

13 DR. DONG: Page 19.

14 DR. CRAIG: So, the ITT percent of healed --

15 DR. DONG: It is 24 percent for the pexiganan
16 group in study 303 and for ofloxacin it is 30 percent.

17 DR. CRAIG: That was not significant though?

18 DR. DONG: That was not significant.

19 DR. CRAIG: It only became significant when you
20 look -- what is the difference with the other group there
21 where you have percents with wound size increased or stayed
22 the same? That was the only place where you saw a
23 difference? Okay. So, in terms of percent wound healing,
24 although it was less it wasn't significantly different. Is
25 that correct?

1 DR. DONG: Yes.

2 DR. CRAIG: Okay. Next question going down the
3 list, was the wound infection score. Yes, Dr. Archer?

4 DR. ARCHER: I think this is really critical, that
5 is, which wounds should be treated topically and which ones
6 should be treated systemically, and where is the border
7 between the two? I think this is a real critical question.
8 It seems to me that the wound infection scores were
9 relatively low. These are relatively benign types of
10 infections that may or may not have healed with good wound
11 care. I mean, that has come up a lot and we don't know the
12 answer to that. So, at what point is there enough wound
13 infection to warrant systemic versus topical therapy? I
14 think this is really critical. I don't know that there is
15 any answer to that from this study but I think that is an
16 important issue.

17 DR. CRAIG: Do we know, is there any correlation
18 between the wound score in those that went on to develop
19 cellulitis or needed to be hospitalized, looking at both
20 arms? I mean, not just limited to your compound?

21 DR. HOLROYD: No, I don't have that data, Dr.
22 Craig, I don't believe, breaking down cellulitis and the
23 other thing you mentioned broken down by wound score.

24 DR. CRAIG: Dr. Gerding?

25 DR. GERDING: I just wanted to comment on Gordon's

1 concern because I think this is going to be an indication
2 that is an exceedingly narrow one, that you have to get it
3 just right in picking your patients for treatment with this
4 regimen, and it is not easy to decide between infection and
5 no infection clinically, and it is not easy to decide when
6 the infection is too severe versus just right for topical
7 therapy, and I think that it will be important to try to
8 generate some guidelines for the prescribing of a product
9 like this, assuming that it is going to market. You know,
10 with my experience with treating these kinds of infections,
11 I would acknowledge that it is difficult, and I think Dr.
12 Lipsky would as well. So, I think this will be a challenge
13 for prescribers to try to judge this correctly in terms of
14 who may benefit and not either over-treat or under-treat
15 with a topical agent. So, I think that is a real challenge,
16 and even experienced clinicians have trouble making the
17 judgment.

18 DR. CRAIG: Yes, or in a way, actually getting
19 down to one of the later questions about the patient
20 population, but the question I still want to focus on right
21 now is do you feel that the secondary endpoint using the
22 change in the wound infection score is important for
23 evaluating the effectiveness of this compound? I see
24 somebody shaking their head. Dr. Gerding?

25 DR. GERDING: I think it is important. I think it

1 consists primarily of the kinds of criteria we use in
2 differentiating an infected from a non-infected lesion. So,
3 I think the change in wound infection score is an important
4 parameter.

5 DR. CRAIG: And the speed at which they change so
6 that, you know, they are similar with the comparator agent?

7 DR. GERDING: I don't think those parameters
8 differed significantly.

9 DR. CRAIG: No, they didn't. I think they are
10 important. That is what we follow clinically.

11 DR. CRAIG: Okay. I see Dr. Norden shaking his
12 head. Anybody else feel that it is a useful test? Dr.
13 Miller?

14 DR. MILLER: I would just comment again on the
15 particular criteria that you have for the score, and Dr.
16 Lipsky responded to that, you know, as far as the tenderness
17 and the pain in the neuropathic foot. It has been my
18 experience that when people with neuropathic feet get pain
19 in an ulcer, frequently it is a more serious infection than
20 just something that is superficial.

21 I would ask about the induration criterion. You
22 know, when you have a markedly deformed foot sometimes
23 induration would be hard to appreciate, plus, these people
24 tend to have stiff joints and their collagen tends to be
25 stiffer also. So, you know, I am not sure. I am thinking in

1 my own mind how I would evaluate that to say, yes, this is
2 indurated and this corresponds to the infection, and then we
3 can become more sophisticated with the warmth, more than
4 just a guess, if we really have a measuring stick.

5 DR. CRAIG: I am a very strong believer that we
6 need to do more of this in a whole variety of clinical
7 infections because there may be differences, agreed that
8 they may be minor but they may be important differences
9 clinically, and if we don't have some way of trying to get a
10 little bit more objectiveness into our clinical assessment
11 it is hard to do. I think the FDA pointed out, at least
12 looking at the data here, that all of the components within
13 this score did change with time, although there was some
14 difference between the two compounds specifically in the
15 wound healing or the reduction in size. Dr. Murray?

16 DR. MURRAY: Yes, I just wanted to comment, those
17 of us who are just sort of shaking our heads, nodding yes --
18 I mean, yes, it is my impression they seem to be useful.
19 Does that mean that I am convinced that every single measure
20 listed under these scores is useful, no, I am not, and I
21 think if you wanted a better opinion on that, if you are
22 really going to sanction it, then you want a panel of
23 doctors of Millers and Lipskys to comment as well.

24 DR. CRAIG: Yes, Dr. O'Fallon?

25 DR. O'FALLON: I have never done this of course,

1 but I have worked on scores for other complex situations
2 such as quality of life, and the problem here is that
3 everything in there may be very important but they may be
4 interrelated to each other and they may not be of equal
5 importance. So, this type of a measure really does need to
6 be validated. There has been some work on it, according to
7 the packet, but has it really been properly evaluated to see
8 whether it is a good measure?

9 DR. GERDING: In studies that I have done we have
10 not used pain, tenderness and induration, which are the
11 things that Dr. Miller is also raising. So, it probably is
12 worthwhile to look specifically at those three at least in
13 terms of how much they follow the other parameters in terms
14 of contributing to that wound score. At least for me, those
15 were the three that caused me the most concern.

16 DR. CRAIG: Dr. Reller, you look like you are
17 about ready to say something?

18 DR. RELLE: To carry this just one step further,
19 with different values of the components of the score it may
20 also be related to where the ulcer is. So, induration may be
21 worthless for a plantar but not for a dorsal ulcer. But to
22 get that refined in how it correlates with wound healing
23 seems to me to be very important because you could develop
24 possibly a score that would give guidance to who should be
25 treated with any compound that might ultimately be approved

1 for this specific indication. That a compound would work
2 when there is infection but not too much infection I think
3 is just too fuzzy to get proper targeting of an approved
4 compound. So, to get the scores validated and simplified to
5 the ones that really do correlate with wound healing would
6 be very important, and there may be appreciable data, just
7 not analyzed, already as a starter that is already in the
8 packet, which just hasn't been looked at that way.

9 DR. CRAIG: Any other comments? And, we are
10 talking here only about the wound infection score which,
11 obviously, people have said is important for deciding the
12 extent of infection, but how about the total wound score
13 which also includes pulses? Does the same thing apply? There
14 were two of them that were used. There was one that was an
15 infection score, primarily to look at the extent of
16 infection and to follow that and, again, that would be the
17 component I think the company would be talking about, that
18 there drug is effective and that total wound score might not
19 necessarily be the primary indicator that should be looked
20 at because that takes also wound healing and wound
21 measurements in there, and that could be something else
22 besides related entirely to infection. So, I am trying to
23 find out is there any differentiation, and for approval do
24 you feel they are both equal, or do you feel that one
25 carries a little bit more weight than the other? Dr. Norden?

1 DR. NORDEN: I think that the wound infection
2 score carries more weight, and the other is even more
3 complex when you start looking at the pulses, the
4 circulation and so on. So, if we could refine wound
5 infection score I would be very comfortable without having
6 to worry about bringing in other variables.

7 DR. CRAIG: Dr. Gerding?

8 DR. GERDING: I agree with Dr. Norden. In fact, I
9 had a lot of difficulty with that overall wound score in
10 terms of trying to figure out how you would do that, and
11 things like brawny edema and pitting edema and duration of
12 the ulcer. It may be useful as a means of teasing out
13 differences in outcome perhaps if you have that kind of
14 data, but when you mix such disparate variables as pulses
15 present, pulses absent, duration of ulcer and brawny edema,
16 I have a hard time trying to sort out a unified concept of
17 what that score means. Individual variables may actually be
18 better, such as duration of an ulcer, in teasing out some
19 kind of an indicator of success or failure in the
20 management, but I have a hard time with the overall total
21 score that is being generated.

22 DR. CRAIG: Okay. Dr. Reller?

23 DR. RELLER: I would like to ask Dr. Miller if
24 there is some role in at least some components that went
25 into the total score to be used to delineate those patients

1 who you would not expect to benefit from this therapy,
2 moving toward the selection of patients. But if there are
3 those who have findings that would preclude a response, even
4 if infected, by the other score, then that would seem to me
5 to be important to delineate.

6 DR. MILLER: Yes, certainly we are dealing with
7 many different factors here, and pulses are very different
8 from brawny edema. I think if a patient comes in for the
9 first time with an infected ulcer and meets the criteria for
10 infection, you know, the first thing that has to be done is
11 that the person has to be evaluated from a vascular
12 standpoint. You know, does he or she have pulses and, if
13 not, what is the severity of the peripheral vascular disease
14 because something will have to be done about that otherwise
15 it won't matter what you do with the infection. Then, also,
16 what is the status of the neuropathy.

17 So, I think the two things that you are
18 evaluating, the sine qua non, are to evaluate the peripheral
19 vascular system primarily and then what is the degree of
20 neuropathy.

21 DR. CRAIG: Just to summarize what I think I have
22 heard, and people can obviously correct me if it sounds more
23 like my own impression than that what you said, it is that
24 in terms of the secondary parameters which were felt to be
25 important in evaluation of effectiveness, microbiologic

1 response was not felt to be one, neither was the combined
2 clinical and microbiologic because it is really driven a lot
3 by the microbiologic response. Change in wound size and
4 depth, especially complete healing, was felt to be an
5 important secondary parameter. The wound infection score and
6 its change over time was also felt to be an important
7 indicator, and lastly, the total wound score much less so
8 because of the variety of other factors that could affect
9 it. Is that sort of the gist? Dr. Danner is going to correct
10 me now. Go ahead.

11 DR. DANNER: I guess what I thought maybe some
12 people were indicating is that the infection score would be
13 important if we knew whether it was useful or not. It hasn't
14 been validated, from what I have heard, and it has to be
15 prospectively validated in some way and be shown to
16 correlate with anything. You don't know what it means. It is
17 great to have one, and to have one that is prospectively
18 validated. I think everybody agrees with that. We just don't
19 know about this particular one.

20 DR. CRAIG: All right. So, again, right now people
21 are interested in it but the question is whether this is a
22 valid one, as has been raised by the committee.

23 Let's move on then to the second question, the
24 potential risk and benefits of pexiganan acetate's clinical
25 use for the proposed indication in the population studied.

1 DR. CHIKAMI: Can I make a comment, Dr. Craig?

2 DR. CRAIG: Sure.

3 DR. CHIKAMI: I think we would like to have you
4 discuss this in the overall context of the discussion you
5 just had, that is, as you have looked across these studies
6 and you looked at not only the primary clinical endpoint but
7 these other sort of analyses that have been done and sort of
8 commented on how important you think these are, how useful
9 these are, and as you discuss part (b) which is related to
10 your sort of overall assessment of the potential risk and
11 benefit of the use of the product, keep in mind sort of what
12 you commented on under part (a).

13 DR. CRAIG: Dr. Norden?

14 DR. NORDEN: I am not sure if this is just going
15 to address part (b) but because I have to leave at 3:30 -- I
16 have a lot of trouble with this whole study and this whole
17 concept, the whole concept of a topical agent, partly
18 because, first of all, I think the company has studied a lot
19 of patients; I think the trials in general are well
20 controlled, well done as far as I can see. I think they are
21 competing with the comparator agent is a very difficult
22 agent to show equivalence to. I would just remind everybody
23 that the 15 percent lower border of a confidence interval is
24 arbitrary, and may be valid and we may have to set some
25 standard but there really isn't anything magical about it.

1 Despite saying that, in general, if you look at
2 the clinical responses, if you look at the change in ulcer
3 size, the cream did not do as well as the systemic agent,
4 ofloxacin.

5 Finally, I would just like to add that I am amazed
6 that there weren't more dropouts in the ofloxacin arm.
7 Taking it is not benign. We have seen some rather miserable
8 reactions, including central nervous system type reactions
9 in patients we have given cipro. or ofloxacin to. And, I
10 think there is something very tempting or appealing about
11 the idea of having an alternative therapy, but I think
12 either Barth or Dale summed it up correctly, to find the
13 population in which I would want to use this agent is still
14 what I am having trouble with. So, I am really on the fence
15 at this point.

16 DR. CRAIG: It was interesting going through and
17 looking at the names of the investigators. You do see some
18 infectious disease people, but the numbers of cases entered
19 at those places are relatively small, and most of them are
20 coming from podiatrists, clinics that deal primarily with
21 feet. It may be that those of us in typical infectious
22 disease practices really aren't seeing these patients since
23 when they get referred to us is when they have not responded
24 to the other things. So, our own vision of what we normally
25 see is not what is really out there in the community. At

1 least, that is the gist I got from looking at the data
2 because, you know, there are very small numbers from people
3 who are working in typical infectious disease practices
4 bringing the people in.

5 Again, if it is 40 percent of them that are mild
6 ulcers, this could be a significant number of them in the
7 regular communities. So, I think we have to be careful of
8 using our own day-to-day experience in our own practice. It
9 may be entirely different than the real disease, this milder
10 disease that is going to be treated.

11 DR. NORDEN: I agree with that, but I think we
12 need something better than either the list of things that
13 the company proposes which they would not treat, and trying
14 to define whom you would treat. I mean, it is easy to say
15 whom you wouldn't treat --

16 DR. CRAIG: Yes.

17 DR. NORDEN: With 104 fever you are not going to
18 use a topical drug; bone showing through an ulcer you are
19 not going to use a topical drug. But who are we going to use
20 it for? Again, I am less concerned about Dr. Lipsky and Dr.
21 Miller and Dr. Gerding making this decision than I am about
22 a lot of people in practice.

23 DR. CRAIG: I can't remember, in their suggested
24 insert did they have anything about the degree of erythema?
25 I think if that is something that is primarily used in the

1 definition of your initial people you would probably be
2 trying to do that; the same thing if there is a wound score
3 as something that you are going to use that would help
4 clarify the individuals a little bit more as well.

5 DR. NORDEN: It just says not extensive
6 cellulitis.

7 DR. CRAIG: Yes. Dr. Murray?

8 DR. MURRAY: While I don't think the cream was as
9 effective overall or equivalent to ofloxacin, I am probably
10 willing to accept a little bit lower efficacy for the
11 benefit of not having a systemic antibiotic and not
12 eliciting or selecting for more resistance to
13 fluoroquinolones. You know, as a well-known expert said it
14 recently, we have blown it with antibiotics, and we could be
15 in big trouble shortly.

16 As far as the potential for some of these patients
17 developing cellulitis, while it would be possible that
18 someone would get such a rip-roaring cellulitis and not come
19 back to medical care that it would have its downsides, I
20 think that is relatively unlikely. These are not people that
21 are likely to be flying across the country away from medical
22 care. They have already come in; I think they will come back
23 if they get sicker.

24 So, at this point in time I would probably be
25 willing to accept a slightly lower efficacy for the benefit.

1 I just wish I had a little better handle on what would be a
2 placebo cure rate because I am not sure that we have actual
3 benefit versus a placebo but I think we probably do.

4 DR. CRAIG: Dr. Parsonnet?

5 DR. PARSONNET: I don't think there has been any
6 demonstration of benefit with this. I think that we don't
7 have a placebo; that we don't know who these patients were
8 who were selected as representative of ulcers in general;
9 that when patients come to see their doctors they are not
10 all randomized, that only a small sample is. The people that
11 may have been randomized may have been the people who would
12 have responded to placebo, and we don't really have any data
13 for that. We really don't have any validation of the
14 criteria that they used to choose people for this study.

15 So, I really can't say from the data that has been
16 presented to us that there is really any benefit to this
17 therapy, plus, we have been told that even as an estimate 50
18 percent of these people might have responded as a placebo
19 effect, and that is taking sort of all-comers, not just
20 people that were selected to be randomized for this study.
21 So, you know, I don't think there are terrible risks to this
22 but I don't see that there is any benefit to this over good
23 wound care, that that has been demonstrated to us.

24 DR. CRAIG: So, you don't see any benefits but you
25 also don't see much in the way of risk?

1 DR. PARSONNET: I don't see much in terms of risk
2 but there is cost. So, unless there are other data to show
3 us who these patients represent, and that these patients
4 really would do better than just plain wound care I can't --
5 I haven't seen that data.

6 DR. CRAIG: Okay. Dr. Lipsky?

7 DR. LIPSKY: Could I just make a brief point? The
8 50-60 percent figure that I gave was for patients enrolled
9 in this study not for all patients that come in, jut to be
10 clear about that.

11 Secondly, I would also ask you to consider the
12 issue of another fluoroquinolone, for example, were applying
13 for a specific indication for diabetic foot infections, they
14 would presumably test themselves, say, against
15 trovafloxacin. You would still not have a placebo-controlled
16 study. You would say we are just as good as, or almost as
17 good as trovafloxacin and, therefore, we would like an
18 indication for diabetic foot infections. I think you are
19 setting the bar unreasonably high to say that when we
20 compare this product against what all concede to be a very
21 good antibiotic for treatment of this infection, and it does
22 almost as well, that that is not good enough.

23 DR. PARSONNET: I have one quick response to that.
24 I don't think that it does really almost as well because if
25 you are saying that 50-60 percent of these people may not

1 have required antibiotics at all, then the group that would
2 have done almost as well is that 30 percent that is
3 remaining. So, in fact, the difference that you are seeing
4 between these groups is much smaller than the actual true
5 benefit that is seen in patients who really need
6 antibiotics. So, I am really not convinced from the data. We
7 have so many people in here who may not have benefited at
8 all from either arm of this therapy that you can't really
9 compare -- you can't tell me what the real differences
10 between ofloxacin and the topical are. So, I am just not
11 convinced from the data that this is any better than
12 placebo, and I am not convinced because I am not sure that
13 the patients were correctly chosen to address that question.

14 DR. CRAIG: To take it just a little bit further,
15 you mean because they were based on an infection score, or
16 what?

17 DR. PARSONNET: Well, because I am not sure once
18 they had debridement that they were really infected. You
19 know, the infection score is a score that is done even
20 before they are debrided, and once you have taken out the
21 infection and thrown it in the trash I am not sure that you
22 need any antibiotic.

23 DR. RELLER: Dr. Lipsky, if one got together a
24 group of experienced clinicians who deal with these
25 infections currently, recognizing, as I think you mentioned

1 earlier, that there has never been a placebo-controlled
2 trial, what would be the agents be that a consensus group of
3 experts would say would be effective in aiding wound
4 healing, coupled with taking the pressure off, debridement,
5 excellent wound care -- effective in infected diabetic foot
6 ulcers as a part of their overall therapy?

7 DR. LIPSKY: So, if I understand your question
8 correctly, in addition to good wound care --

9 DR. RELLER: Yes.

10 DR. LIPSKY: -- what anti-infective agent would an
11 experienced clinician consider to be appropriate for
12 treating an infected ulcer --

13 DR. RELLER: A consensus group, you know, not only
14 just yours --

15 DR. LIPSKY: Right.

16 DR. RELLER: -- but, say, five experts together. I
17 have my own list from what has been published, ad so on, but
18 I am interested in seeing what you would come up with.

19 DR. LIPSKY: Sure. Well, if you ask me this about
20 six to eight months from now I would be able to give you a
21 better answer because I am actually chairing an IDSA group
22 on developing guidelines for diabetic foot infections, and I
23 intend to ask that question of the kinds of people you refer
24 to.

25 My own feeling is that products should be tested

1 in the clinic in order for me to recommend them. So, I can
2 tell you the agents that have been tested in studies:
3 cephalexin and clindamycin have been shown to be 85 percent
4 effective in treating similar type patients to the patients
5 we talked about today, and either of them, it seems to me,
6 would be a reasonable antibiotic agent. Trovafloxacin has
7 certainly shown itself to be effective, and the comparator
8 in the trovafloxacin study, Augmentin, or amoxicillin-
9 clavulanate has shown itself to be effective. I think
10 ofloxacin and ciprofloxacin have been widely used. I am a
11 little more comfortable with ofloxacin the ciprofloxacin,
12 although I think they have probably been overused.
13 Levofloxacin perhaps would be a better choice. So if you ask
14 me among the other quinolones besides trovafloxacin, perhaps
15 levofloxacin would be the agent that I would choose.
16 Dicloxacillin is still something that I sometimes use in a
17 patient who has not recently had any other antibiotic and it
18 is highly unlikely they have anything other than staph. or
19 strep. but I don't often feel comfortable enough to just use
20 dicloxacillin. I would be interested to hear your list and
21 maybe have you sit with our group.

22 DR. RELLER: Well, my list was only the first four
23 that you had down there. I ask the question because I would
24 like to second some of the things that Dr. Parsonnet said.
25 Dr. Gerding said he was surprised that this compound did as

1 well as it did, but ofloxacin is not approved for this
2 indication. I recognize that at the time these studies were
3 initiated the choices were more limited. So, I mean, you
4 know, not to make too much of the point but I don't think it
5 would be in the top tier of agents, and I have a nagging
6 suspicion that these things don't look too dissimilar but if
7 there would be any differences it is on the lower wound
8 healing side. And, it may be that neither one is
9 particularly good and, therefore, they don't look much
10 different from each other.

11 What I would like to see is a validated wound
12 score that was specific for the location, or correlated well
13 and served the purpose for the location for this and other
14 topical agents that may follow because the portion of the
15 patients who would fairly be good candidates for such a drug
16 are those that have some infection but not too much
17 infection, and with a wound infection score, I think having
18 a placebo-controlled trial to complement what has been done
19 already is very important. If it is a lot better than the
20 vehicle in which this compound occurs, or is applied, it
21 shouldn't be very difficult with a validated wound score to
22 show that. Without it, I feel I cannot, based on the data
23 presented, say whether it works as well as nothing or not.

24 DR. NORDEN: Barth, my only disagreement, I guess,
25 is that, again, the company did the trial -- well, let me

1 put it differently, if the lower confidence limit had not
2 exceeded 15 percent in one of two trials, would we be
3 sitting here and having a discussion? We might have a
4 discussion about the labeling and so on, but we would have
5 to say that the product met the standard that the agency has
6 set up, I believe.

7 I am equally unsure that this is really better
8 than placebo, but I am comfortable that ofloxacin is an
9 effective agent, and I am comfortable that the numbers that
10 we saw with ofloxacin in terms of clinical response are
11 comparable to those which we have seen before with
12 clindamycin and with cephalexin. So, I think there are
13 certain reasons why I am uncomfortable with just sort of
14 saying we ought to be doing a lot more studies. There are
15 over 800 patients who have now been studied. So, I am not
16 quite sure -- I don't think we would do a placebo trial
17 because I would be very uncomfortable unless I could define
18 the population very carefully and was not afraid of hurting
19 them.

20 DR. RELER: It just seems to me that to use this
21 compound appropriately one has to have very precise
22 indications for the patients who might benefit, and it is
23 for that very reason that I am unsure that the difference
24 with placebo in the very patients who could be narrowly
25 enough defined would be legitimate candidates for therapy. I

1 mean, we want a forthright opinion and I am not very excited
2 about it. I am sorry that there are over 800 patients but I
3 am not very excited about the comparator and what we are
4 trying to assessment from the comparator with the topical
5 agent.

6 DR. MURRAY: I just wanted to say something about
7 that because, in fact, whether people are using ofloxacin,
8 levofloxacin or ciprofloxacin would basically have depended
9 on at what period of time and what your pharmacy had bid to
10 purchase. We switched from ciprofloxacin to ofloxacin for
11 every infection strictly on what was bid to our pharmacy,
12 and whether it was twice the MIC or half the MIC and twice
13 the blood levels was not taken into account whatsoever. Did
14 that make a difference? I don't know but I am quite sure
15 levofloxacin has been widely used for this sort of
16 infection. How effective it is I am not sure, but I am sure
17 it would qualify as a standard of care.

18 DR. CHIKAMI: Dr. Craig?

19 DR. CRAIG: Yes?

20 DR. CHIKAMI: Can I just comment on that, just to
21 follow-up on the conversation and what Dr. Norden had to
22 say? I guess at the time these trials were designed, in
23 fact, there were no approved agents with this indication.
24 There was extensive discussion between the pharmaceutical
25 company and the agency about what would be a reasonable

1 active control trial, and I think the discussions were in
2 the setting that it was felt at the time that an active
3 control trial was an appropriate design in this indication,
4 and that it, in fact, may have been difficult -- and, again,
5 I am trying to sort of paint the context of the situation of
6 when these trials were designed, that an active control
7 trial was an appropriate design.

8 Now, that is not to say that the issues that are
9 being raised about what would, in fact, the response rate be
10 in patients with very mild infections with good debridement
11 and other sort of local care be, and I think it is very
12 difficult to get a handle on that, as our experts sort of
13 commented. Both Dr. Lipsky and Dr. Miller have commented
14 that that number is very difficult to get a handle on. So,
15 just to provide you with that perspective that, in fact,
16 these trials were designed in discussion with the agency,
17 and that with all of the limitations an active control trial
18 was sort of the design settled upon, and that this was sort
19 of the comparator agent that was felt to be appropriate at
20 the time.

21 DR. CRAIG: Yes, Dr. Chesney?

22 DR. CHESNEY: Did you decide on a score of seven
23 for some reason? In other words, if there was a score of ten
24 were those patients automatically eligible for oral therapy
25 or IV therapy?

1 DR. CRAIG: The score was not an entry criterion.

2 DR. CHESNEY: Not ever having seen diabetic foot
3 ulcers, I wonder what is known about the natural history. I
4 mean, would a score of seven normally improve without
5 extensive therapy, or is anything known? And, why would it
6 be unethical to use placebo? I saw that word somewhere and
7 Carl indicated some concern about that, and I am just
8 wondering why it would be of concern if the more seriously
9 ill patients automatically got systemic -- I mean, they
10 weren't included in the study.

11 MR. BOSTWICK: Not speaking specifically about
12 this study but just historically, in the last few years we
13 have had a difficult time getting sponsors to agree to
14 placebo-controlled trials in infection disease processes
15 unless it is a very mild -- impetigo perhaps. I think for
16 reasons of liability they are reluctant to do it. So, maybe
17 rightly or wrongly, we have kind of backed away from a
18 placebo as a satisfactory control group, except in specific
19 cases.

20 DR. CRAIG: Yes, you have brought it back for at
21 least acute bronchitis now, that those have to be placebo-
22 controlled, but that is the only one I know where you do
23 require it. Other comments?

24 I personally think that ofloxacin as the active
25 ingredient is not a terrible agent for Gram-positives and

1 for some of the anaerobes. Again, anaerobic coverage, as Dr.
2 Lipsky's studies have suggested, is not that critical
3 anyway, especially with debridement, and those things
4 oftentimes are going to disappear on their own. So, I am
5 looking more at the Gram-positive and the Gram-negative
6 organisms and, in that regard, I think it is a reasonable
7 agent. So, I did not have the trouble that you had, Barth,
8 with the comparative agent.

9 DR. PARSONNET: Just one quick comment. I don't
10 think that anybody would necessarily advocate a real placebo
11 control but you are doing aggressive debridement, which is
12 not exactly a placebo, and I think if you do aggressive
13 debridement and you see at the end that you have actually
14 got clean margins and things don't look very infected, and
15 you try to take care of the infection by debridement, that
16 may be actually a good control group to have, and then have
17 the other group be a group that has the active agent.
18 Because the question here is not whether doing nothing is
19 the right thing to do; the question is whether doing surgery
20 alone is adequate.

21 DR. MURRAY: I guess the same could be said for
22 treatment of abscesses because if we drain most
23 intrabdominal abscesses they may eventually heal in, but we
24 wouldn't do it that way because antibiotics would facilitate
25 the course and what we are saying is we really don't know if

1 they facilitate the course here.

2 DR. PARSONNET: You can look at this ulcer every
3 single day and say is it getting worse or is it getting
4 better. I mean, you are looking at it every day and you can
5 make an assessment every day.

6 DR. CRAIG: But these patients were treated as
7 outpatients so we weren't looking --

8 DR. PARSONNET: Yes, but they are looking at it. I
9 mean, they are putting cream on it every day. You can tell
10 them, "tell us if it's getting better; call us tomorrow if
11 it gets red." I mean, they have an opportunity to look at it
12 every single day, unlike an intrabdominal abscess which will
13 come back and bite you, you know, if you are not taking care
14 of it.

15 DR. CRAIG: Yes, Dr. Danner?

16 DR. DANNER: I think the problem here is this is
17 kind of a tough one. You know, the data is not, in fact,
18 clear-cut in either direction but, yet, on the other hand,
19 you don't want to throw the baby out with the bath water,
20 and you don't want to set new standards at this point which
21 you are going to hold the drug to.

22 In terms of equivalence -- I think I agree with
23 everyone here that efficacy is very hard to evaluate here.
24 Equivalence has a clear statistical definition and that was
25 what was attempted here, to do studies that showed

1 equivalence. From my understanding of the data, one study
2 doesn't show equivalence and the other study shows
3 equivalence though there is another difference between the
4 two studies. In one study you sampled the data and you found
5 that there were some discrepancies about how people would be
6 rated, and it was like 18 percent. So, you redid the data
7 and in redoing the data, it looked to me like it went
8 against the drug, the pexiganan a little bit.

9 MR. BOSTWICK: But even if one used the original
10 patient cohort it would have failed the per-protocol
11 population. It appeared a little bit worse after we redid it
12 but it came out pretty much the same.

13 DR. DANNER: In the second study there was a lower
14 rate of discordance between your classification and the
15 company's. It was only 10 percent.

16 MR. BOSTWICK: Correct.

17 DR. DANNER: But that data wasn't reclassified
18 because it was a lower rate.

19 MR. BOSTWICK: Right.

20 DR. DANNER: But it seems to me that it is not
21 inconceivable that if that data was redone it might either
22 get stronger or weaker, and it might help us in some way.

23 MR. BOSTWICK: It may. I have no idea. We just set
24 sort of an internal standard that if we found a 10 percent
25 error we would accept that data. Another kind of reason for

1 doing the first study is that it seemed marginal to begin
2 with. The second study seemed more solid and we thought,
3 well, if we do find errors it is less likely to change the
4 results. But we can do the second study and see what comes
5 out.

6 DR. DANNER: I don't know how other people feel
7 but since this is all so borderline, I guess I would prefer
8 that the second study was reclassified just to see if it
9 helps us in any way in terms of making a decision here,
10 because I am not certain what to do. I guess, I ultimately
11 think that the two interventions were not quite equivalent.
12 They are close but they are really not quite equivalent, and
13 if they are not really equivalent then, you know, it doesn't
14 meet the original bar that was set.

15 DR. CRAIG: Right. But it appeared, at least in
16 terms of background and wound size, that there were
17 differences in that first study that were against this
18 compound. So, the question is could those differences have
19 explained the reason that equivalence was not seen. Were
20 those patients that had those pre-entry criteria in those
21 that had the larger wound sizes have a lower response and,
22 therefore, because they were unevenly distributed between
23 the groups, impact on the data. At least from the logistics
24 analysis they did, looking specifically at that group, they
25 couldn't pull out that that was a legitimate explanation,

1 although when you looked at sort of the dirty way of looking
2 at it, there was a hint that maybe it might have contributed
3 to it.

4 DR. DANNER: I may be incorrect about this, but
5 even in the second study, the 304 study there was still the
6 issue of wound healing and closure where the drug didn't
7 look as good.

8 DR. CRAIG: Right.

9 DR. DANNER: That was in both studies. So, there
10 are signals from both studies that maybe it is not quite as
11 good, though I agree that the 303 study showed the biggest
12 problem. So, I don't know. You know, it is just very fuzzy.
13 I don't know what to decide but I guess since one study was
14 redone and the other one wasn't reclassified and looked at,
15 maybe we would get some help from that. Maybe the
16 statisticians could tell me whether that is a reasonable
17 thought or not. I don't know.

18 MR. BOSTWICK: We don't know. Basically, one of
19 the things we thought about was that since 303 was done
20 first the technique in 304, in terms of assessing patient
21 results and just basically entering the data, was better. If
22 I had to guess, I would say we would reclassify study 304
23 and still come out with the products not significantly
24 different in the primary efficacy variable, but we can sure
25 do it and see what happens.

1 DR. CRAIG: Yes?

2 DR. HOLROYD: If I may, I would just ask if this
3 is a correct statement of Mr. Bostwick and the medical team,
4 that the reclassification mostly involved having a per-
5 protocol group where the follow-up visit window was
6 emphasized as a criterion for being in the group, and that
7 we emphasized end of treatment and day 10 visit windows, and
8 your group included or excluded not based on those but on
9 the follow-up visit window, and that was the principal
10 difference for this additional per-protocol population in
11 303.

12 MR. BOSTWICK: Right, the principal reason for
13 changing patients was visit window.

14 DR. CRAIG: Could we go on to the next one? I
15 think this has summarized some of the risks I heard that
16 some people voiced earlier, that this could go on and you
17 might have a patient that didn't deserve to be on topical
18 therapy and might have a cellulitis, but I think if you look
19 at the data that was actually presented it didn't look, at
20 least to my mind, that that resulted in a significant number
21 of hospital days or an increased number of amputations
22 compared to the people that were receiving the ofloxacin.

23 On the other hand, Dr. Reller suggest, well, they
24 weren't on a very good system agent too, so that could
25 explain why there were some patients that still, even with

1 that drug, needed hospitalization.

2 I think in terms of other kind of risks of
3 resistance that did not seem a concern with the people. In
4 fact, that was one of the benefits that I think I heard some
5 of the people talk over some of the time that we have been
6 talking, the ability to use an agent for which resistance
7 has not developed as a benefit compared to a system agent
8 where we have had experience with the development of
9 resistance.

10 In terms of benefits, summing what I think I heard
11 from the group, was that some felt there is something there,
12 maybe not quite as good as seen with the comparator, to the
13 response that this may not even be different than placebo.
14 So, in terms of the benefits, I think the committee right
15 now feels sort of from some effect to no effect. So, I don't
16 think there is any consensus that I have heard as yet in
17 terms of the response.

18 So, going on now, based on the discussion, do the
19 data support the safety and efficacy of pexiganan acetate?
20 Before everybody starts to disappear on me we have to get
21 some votes or at least some comments on this. Carl, you are
22 going to be leaving fairly soon so you had better get your
23 comment in.

24 DR. NORDEN: I think the data support the safety;
25 I don't think they support efficacy well enough to feel

1 comfortable. I think that the patient population is, for me,
2 still the hardest thing to define, and I think it could be
3 defined by a wound infection type score less than such-and-
4 such. That needs to be validated, as people have said, which
5 I think is where further studies would be -- I would feel
6 comfortable if you could validate a wound infection score
7 that I would use the cream in this population because I
8 don't think it has to be equivalent to a system agent and I
9 really don't want to keep on using ofloxacin.

10 So, I can't vote to approve it. I would not
11 recommend approval at this point.

12 DR. CRAIG: But you are saying that they don't
13 necessarily warrant more trials but more validation --

14 DR. NORDEN: Yes.

15 DR. CRAIG: -- of the patient population that one
16 could use an infection score, or something like that, to
17 identify the population.

18 DR. NORDEN: Yes. I don't really see going through
19 the expense of another trial, either placebo controlled --
20 although I do think Julie is right. Would I feel comfortable
21 using debridement only, vigorous debridement only and off-
22 loading versus vigorous debridement, off-loading and the
23 cream as a comparative trial -- that is intriguing, but I am
24 still uncomfortable with outpatients. I know they are
25 looking at it themselves but infection in diabetics can move

1 very quickly. That is not a "yes" vote I guess.

2 DR. CRAIG: Other comments? Do you want to add
3 anything else, Julie?

4 DR. PARSONNET: No, I don't. I have to leave a
5 little early also. I basically agree with everything Dr.
6 Norden said. I feel that there is no evidence presented that
7 this is unsafe. In fact, it looks like it probably is safe.
8 I think that there has really not been any good data
9 presented, to me, that indicates that it is efficacious, and
10 I would love it to be efficacious because I would love
11 people not to use quinolones to treat this type of infection
12 if they could do something topically.

13 I would favor trying to do some sort of aggressive
14 surgical debridement trial with very close follow-up of
15 these patients, and whether you have the nurse go to their
16 house every day to take a look at it or however you set it
17 up, I think it would be helpful to have something like that.

18 I think there is a possibility actually that does
19 have some risks to it that have not been mentioned because
20 these people are now manipulating this ulcer every day. They
21 are wiping cream on this ulcer every day, and that may
22 actually have deficits compared to actually having it
23 wrapped up in one of these protective boots for the span of
24 a week. So, we actually don't even know from the data
25 presented whether the cream has risks because some of the

1 risk to it may be related to something that they did in both
2 arms of the study.

3 So, my sense is that it would be wonderful to show
4 that this works, and I would be very enthusiastic about it
5 if we could avoid oral therapy with these very potent
6 antimicrobial agents, but I am not convinced by the data
7 here that there is any efficacy shown at this point.

8 DR. CRAIG: Okay. Dr. Chesney?

9 DR. CHESNEY: I agree with Dr. Norden and Dr.
10 Parsonnet. I also would love for this to work for the
11 reasons that Dr. Parsonnet just said, that we didn't have to
12 use very powerful broad-spectrum other drugs to treat. But I
13 think with just a little bit more effort, even if it meant
14 seeing the patients every day for the first few days and not
15 just letting them make a report, it would be much more
16 convincing to show that it was better than just debridement
17 alone.

18 DR. CRAIG: Dr. Murray?

19 DR. MURRAY: Dr. Archer left his written comments
20 that are in agreement with what has just been said. I guess
21 I am perhaps going to be a minority opinion. I am going to
22 say I think it doesn't look as efficacious as ofloxacin but
23 I think it is pretty close to being equivalent to a standard
24 of care. So, yes, I think it is safe. I think it probably is
25 efficacious. It hasn't been shown fully equivalent in the

1 different studies but in one was. In what population should
2 it be used? In relatively mild infection. If called to a
3 vote, I would probably go with approval, or a recommendation
4 for it.

5 DR. CRAIG: And what were Dr. Archer's comments?

6 DR. MURRAY: His were the same as the other three:
7 yes, safety; no, efficacy; don't know if no treatment works
8 in this group; what population -- very mild infection. Can
9 physicians really make this distinction? What studies would
10 you recommend the applicant conducting? Placebo-controlled.

11 DR. CRAIG: Okay. Dr. Reller, do you want to
12 comment? Or, we can just take a vote of the remaining
13 people, if you want to do it that way.

14 DR. RELLER: Well, I do agree substantively with
15 what has been said. To me, one of the most important reasons
16 for having a tight design with the wound validation score is
17 that then one would have the objectivity to say this
18 compound, with all of these other benefits for antimicrobial
19 resistance, etc., actually works and doesn't have these
20 other downsides. So, it just seems to me that one could make
21 the case for using it much more forcefully if one had a
22 database that would eliminate the concern that has clearly
23 been shown about whether it works at all. So, it is the
24 efficacy solidification, and we have two trials, one
25 especially found wanting. So, I would not approve it on

1 demonstration of efficacy.

2 DR. CRAIG: Okay, but safety?

3 DR. RELLER: That is fine.

4 DR. CRAIG: That is fine? Okay. Dr. Miller, any
5 comments?

6 DR. MILLER: I think from what we know at this
7 point it does appear to be safe. I would just comment that,
8 you know, there are those people whom you debride and they
9 still have some erythema around. You know, they still have
10 clinical infection and those would be the types of people
11 that we would be talking about for this product.

12 I agree with Dr. Murray. I think there is some
13 efficacy as I look at the trials, but there has been a lot
14 of statistical maneuvering and I can't comment with any type
15 of cogency on those because I just don't understand all of
16 that. But I do think there is some efficacy, and I think it
17 would be really good if we had a superphysiologic agent, as
18 this appears to be, for use.

19 So, my concern is that patients can't evaluate
20 themselves, especially this population. If you look at the
21 data here, you know, they tend to be older. Many of them are
22 heavy; many of them don't see well; and they can't see the
23 bottoms of their feet. So, if you are going to evaluate
24 something critically you really need someone to do it for
25 them, and we see a lot of these folks and I just don't think

1 they are capable of doing that.

2 My concern is, like other products that are
3 available, that, you know, people will use something like
4 this without going through the other maneuvers -- without
5 the debridement, the off-loading and checking the vascular
6 situation. But I guess we would have to live with that. I
7 would vote for approval.

8 DR. CRAIG: How is your feeling about a placebo-
9 controlled trial? Do you think one could be done? Or, are
10 your concerns that people can't see, and things like that --

11 DR. MILLER: I think if it were done someone would
12 have to be looking for them, and I think someone should
13 almost be applying the medication for them because I think
14 compliance is a big issue. And, we are dealing here with
15 non-life threatening diseases and I think the comment was
16 made that, you know, you observe and if it looks as if
17 something is worsening or changing then you intervene. So,
18 it would require, I think, very close scrutiny. But that
19 would be the ideal, certainly.

20 DR. CRAIG: You can't vote, Dale, but if you want
21 to have any comment?

22 DR. GERDING: Yes, I will comment. I know I am not
23 going to vote but I will tell you how I would vote. I
24 actually would have added to Dr. Lipsky's list trimethoprim
25 sulfa as an effective oral agent for treating these kinds of

1 infections. I have used it extensively. So, I would be
2 completely comfortable with the comparator agent ofloxacin
3 as being an effective treatment here.

4 I share everybody's concern about good debridement
5 plus any kind of antimicrobial therapy versus good
6 debridement alone as an efficacy test here. We don't have
7 that data. I think the trial would be almost as big as the
8 trial we have already witnessed here, the two trials, in
9 terms of trying to prove that topical is going to be better
10 than just the debridement alone. So, if you want that done,
11 you are asking for a fairly large undertaking. That is my
12 personal opinion because the numbers here statistically
13 could be quite large before you were able to tease out the
14 benefit of a topical, potentially at least, depending on how
15 you select your patients.

16 I think the biggest concern I have is that the
17 topical product failed to show equivalence in the primary
18 outcome indicator of study 303. That, to me, is of most
19 concern but I think it is showing benefit in these patients.
20 That is my own personal opinion because we don't have a
21 placebo or untreated trial here, or surgery alone trial.

22 So, I think it is advantageous. I would be
23 inclined to suggest approval, although I must say I still
24 don't know the answer to the questions that are being raised
25 about how much we can do to treat patients without any

1 antimicrobial therapy. If these patients clearly met the
2 criteria that were set here for mold infection, then I think
3 they needed to be treated with an antimicrobial agent of
4 some kind. I don't know to what extent that is true but we
5 certainly saw an analysis in which we eliminated the low
6 score, the people from the analysis, and I don't think that
7 substantially changed the outcome. Correct me if I am wrong.
8 You did do that, right? You eliminated the lower scoring
9 wound infection patients in one of the analyses?

10 DR. ROBERTS: Four and less.

11 DR. GERDING: And that did not alter the outcome
12 statistically. Is that correct?

13 MR. BOSTWICK: Slightly but it didn't make a
14 statistical difference.

15 DR. GERDING: So, I think the product is
16 efficacious. I share Dr. Murray's concern about inducing
17 resistance with a lot of oral therapy. On the other hand, I
18 am concerned about putting a topical agent on that may be
19 used systemically at a future date and developing resistance
20 to that too. So, that has both sides to it but I am inclined
21 to think the product is helpful, but I am very concerned
22 about how it will be targeted for use if approved; that it
23 will be misused I guess is what I am concerned about.

24 DR. CRAIG: Dr. Parsonnet?

25 DR. PARSONNET: I hate asking the group to do a

1 placebo trial after they have done a lot of work already so
2 I understand why people might be reticent to do that. And, I
3 would like to suggest just one other alternative way to
4 analyze the current data, if they have this available, and
5 that is to look at the infection status after debridement
6 and then exclude the people who really have no evidence of
7 infection either after debridement or on day three so that
8 you really have people who have infection once surgery has
9 eliminated what it can eliminate. And, if there still seems
10 to be fairly good clearance of that infection afterwards,
11 then I would feel more favorable in terms of it being
12 efficacious. If much of the effectiveness is due to surgery,
13 or the predominance of it -- if the vast predominance of it
14 is due to the surgery I think they would have to do a
15 placebo trial.

16 DR. CRAIG: Dr. Rodvold?

17 DR. RODVOLD: Well, I have looked at this multiple
18 ways coming in and while I have sat here, and I have
19 probably come closest to Dr. Murray and Dr. Miller. Looking
20 at the indication in a topical product for these types of
21 patients as a consumer, I think with the data that it is
22 safe. I think it will prevent potentially more increase of
23 resistance because it is a topical.

24 The efficacy data is a little bit rocky but I
25 think that in light of the number of people that potentially

1 would use the product, I am kind of favoring it. My
2 stipulation goes back to the question I asked right in the
3 beginning about mild, moderate and severe, identifying that,
4 and I think that is really the problem that leads us to
5 labeling issues here. The agency is going to have to come
6 back to the score and try to come out with a score to lead
7 people to identify and use that as a marker, or surrogate,
8 or whatever to give people an idea of whether or not this is
9 working.

10 In light of the trials that were set up and agreed
11 upon, I think that is what pushes this forward. They agreed
12 that this is the comparator, and I think ofloxacin is a
13 comparator that is valid here. My concern though, like Dr.
14 Miller's, is that people will start switching the order of
15 treatment. The way the presentation by Dr. Lipsky was, was
16 supportive therapy, surgical procedures and antibiotics
17 being three, and it needs to stay still three despite giving
18 a topical drug. And, I think it is very, very important that
19 that comes across in the insert to people; that that
20 information gets out there and is constantly brought to the
21 surface.

22 If approval does occur, then I think they do need
23 to come back and try to continue to help identify the right
24 candidates and follow that, and continue to follow if
25 resistance can develop at all, and not to stop where they

1 are at this point. So, I would move ahead with it.

2 DR. CRAIG: Okay. Dr. O'Fallon?

3 DR. O'FALLON: I was not very happy with the
4 analysis because when I got done I had so many questions.
5 When we try to do an equivalence trial, basically the idea
6 is that we do it in the per-protocol. The definitive
7 analysis of the primary endpoint is in the per-protocol, the
8 reason being that you take out the people that didn't -- you
9 know, presumably they were not treated per-protocol so all
10 they are doing is diluting any effect, and they tend to make
11 it look more equivalent because they move any real
12 differences closer to each other. That is the philosophy
13 behind doing it in the per-protocol.

14 Now, the problem for me right from the get-go has
15 been the fact that there has been an unequal loss in those
16 treatment groups. I am going back in here and there are as
17 many as 21 or 24 more people dropping out of the cream
18 active group as opposed to the oral active group in several
19 of these analyses. That bothers me. Who went out? Who was
20 left? We saw the baseline characteristics of the people that
21 started the trial but we didn't see the characteristics of
22 the people who were in the per-protocol comparison. So, we
23 need more information in order to understand what we saw.

24 In the final analysis though, those definitive
25 analyses said that this was not equivalent. That is the

1 problem, that the cream was not equivalent according to the
2 standard analysis.

3 And, the magic 15 or 20 percent -- I think that is
4 an FDA thing. In our medical center when we design
5 equivalence trials, what we do is we sit down with the
6 medical people and we say, okay, how much loss, how much
7 drop in effectiveness would you consider acceptable given
8 the cost, the harassment, the money, whatever it is, the bad
9 things that are associated with the newer therapy? We set
10 that and then decide what our level has to be, what the
11 sample size has to be to have adequate power to detect that
12 difference. I don't know, is 15 percent -- going from 75
13 percent efficacy to 60 percent, is that okay in this
14 disease? Going from 70 to 55 or 50, is that okay in this
15 disease? That is the bottom line in doing an equivalence
16 trial.

17 As for the placebo thing, I came in here and there
18 was a statement saying that it would be unethical to do a
19 placebo trial and, yet, the first thing I hear this morning
20 is that maybe there is a whole group of that don't need
21 anything more than just debridement or, you know, surgery
22 and good care. That sounds like maybe a placebo trial would
23 be okay in a certain population. I don't know. That was a
24 question.

25 DR. CRAIG: I think that was more or a "no."

1 DR. O'FALLON: That is a "no."

2 DR. CRAIG: Dr. Danner?

3 DR. DANNER: Could I ask three questions?

4 DR. CRAIG: Sure.

5 DR. DANNER: In terms of the animal studies that
6 have been done, has a placebo trial looking at clinical
7 efficacy been done in animals? I saw microbiologic data. Is
8 there also data comparing this to placebo in an animal wound
9 infection, that it cures the infection and that it is
10 different than just giving wound care?

11 DR. CRAIG: I would ask the sponsor.

12 DR. HOLROYD: We conducted a number of infection
13 models which I believe showed the anti-microbiologic
14 efficacy in addition to the ex vivo studies of pig skins, a
15 number of live animal studies with infections placed into
16 wounds with Pseudomonas, Staph. aureus. Obviously, those are
17 all so detailed data, and there was a reduction in organisms
18 compared to vehicle, for example, if that is what you are
19 asking.

20 DR. DANNER: No, I am asking if there was a
21 clinical effect. You know, the fact that you reduced the
22 number of organisms compared to, I guess, a placebo -- I saw
23 that data, but if you give an animal a wound with a small
24 surrounding cellulitis, is it different than just giving
25 wound care?

1 DR. HOLROYD: As far as I know, we didn't do any
2 kind of wound scoring system for these wounds in the animals
3 at that time.

4 DR. DANNER: Okay. The next question for the FDA,
5 you know, everybody agrees it is safe but what is not agreed
6 on is whether there really has been a demonstration of
7 either equivalence or efficacy. Is there a lower level
8 approval? In other words, does it have to be efficacious?
9 Could it be, like, you know, safe and may be a useful
10 adjunct?

11 [Laughter]

12 MR. BOSTWICK: Dr. Chikami will answer that.

13 [Laughter]

14 DR. CHIKAMI: Thank you, Dave. The regulations
15 speak to adequate and well-controlled studies providing
16 substantial evidence for safety and effectiveness for the
17 intended use. I think what you are getting at is what the
18 intended use clause is. Under most circumstances, certainly
19 for anti-infectives, in those situations where it is felt
20 that a placebo-controlled trial is not ethical, in an active
21 control setting we draw the conclusion that a product has
22 demonstrated effectiveness and safety and the indication is
23 what is called a first-line indication.

24 There are circumstances in other divisions within
25 the agency where a product may get a second-line indication,

1 and this may be for a number of reasons. That has generally
2 not been the practice within anti-infectives.

3 DR. DANNER: Okay. Then the other question, and I
4 don't know if this can be answered, but are there other
5 ongoing studies or clinical trials with this agent where
6 approval for other indications is being sought? Can that be
7 asked?

8 DR. HOLROYD: No, it is not.

9 DR. MURRAY: In their packet, they did use
10 essentially a placebo in one study where they used
11 gentamicin cream against a gentamicin organism but they were
12 looking at wounds in swine that had organisms inoculated.
13 They weren't looking at wound healing. In that case, where
14 they used a gentamicin susceptible organism they reduced
15 Pseudomonas. When they used a gentamicin resistant organism
16 with gentamicin they didn't reduce Pseudomonas. That would
17 essentially be a placebo but still just looking at bacterial
18 load, not wound healing.

19 DR. DANNER: Thanks. I guess I think it is safe
20 but I ultimately don't think you can, in the strictest
21 sense, make the statement that effectiveness has been
22 demonstrated. I think it probably does do something but I
23 don't think it has been demonstrated.

24 DR. CRAIG: Okay.

25 DR. DANNER: Shall I comment on other studies?

1 DR. CRAIG: I might as well get my comments out
2 first as the final person. In my looking at the trials, .
3 looking at the primary endpoint, as I mentioned earlier, my
4 one concern is with the one that did not show equivalency.
5 Whether that could be explained by the abnormalities or the
6 differences in randomization among the groups, although the
7 logistic regression didn't clearly show that there were some
8 suggestions. So, I am still not convinced that the reason
9 that one did not meet that endpoint was because of the
10 significant difference between the groups in some of those,
11 the initial size of the ulcer and also the previous
12 underlying disease.

13 I also am a little bothered by the data suggesting
14 that t here is less healing, but, in my mind, can almost
15 sort of dissect those two apart and say that they may be two
16 separate things. And, what I would really want the
17 investigators to do is actually to go to some animal models
18 and see if these compounds actually do have any inhibitory
19 effect on wound healing, starting off with an infected
20 wound, to see if there is any slowing of the wound healing
21 which would then account for the difference that was
22 observed in both of the studies.

23 But in terms of its activity, I think the drug
24 does have some efficacy. It may not be quite all the way to
25 ofloxacin from that one study, but it is borderline, and

1 with the background, I would probably would have voted yes
2 for efficacy and, again, yes for safety. But even with
3 saying yes there would have been some questions that I would
4 like the sponsors to answer. Specifically, the one that I
5 would want to look at is if they could show any evidence
6 that this drug had any impact on wound healing because, if
7 it did, then that would make me feel even stronger that that
8 was what you were seeing when you were looking at that as an
9 endpoint, but that would be also something that you would
10 want to at least put some caution in any package insert that
11 the drug has as an addition to its anti-infective effect.

12 So, if we total those all up, I think it was four
13 yes and seven no. Those are the numbers that we have sort of
14 coming up. Although, I must admit, Dr. Norden's no was sort
15 of a yes/no in that he didn't feel that they needed to do
16 other studies but that what needed to be done was to
17 standardize or validate the infection score so that he could
18 look more at trying to ensure that the package insert
19 identified the right subset of patients that this drug would
20 be used for. So, no matter where we cut it, we don't reach a
21 majority in favor.

22 Other studies that you would recommend to the
23 applicant -- I think we have heard some. One of them was a
24 placebo-controlled trial. How many would be in favor of
25 that? Assuming it could be done?

1 [Show of hands]

2 There is a good majority on that, if it could be
3 done. Obviously, it would be nice but I am not sure that it
4 can be done. Yes, Dr. Reller?

5 DR. RELLER: Earlier Dr. Gerding said -- if I got
6 this right, Dale -- that the numbers of patients that would
7 be required to show a difference between placebo and this
8 compound would be prohibitively large. Is that an accurate
9 paraphrase?

10 DR. GERDING: Probably comparable to one of the
11 studies that has been done here.

12 DR. RELLER: When one says how much would have to
13 be done to show a difference tells me that it is all the
14 more important to demonstrate a difference, particularly
15 when we are talking about a very defined set of patients who
16 might benefit. And, if they have no infection they are not
17 going to benefit from an antimicrobial compound, presumably;
18 and if they do have infection they can have so much
19 infection that a system antimicrobial agent is necessary.
20 That is the dilemma that I think is one that is worthy of
21 further consideration to delineate how much benefit there
22 is, in part with the wound score, to delineate those
23 patients who would be appropriate recipients of this agent.

24 DR. GERDING: My problem with a placebo-controlled
25 trial is using debridement as an indication because I think

1 there are variations in debridement. When you give somebody
2 a pill you have given them one pill. Sure, there may be some
3 variations in absorption but I think the amount of
4 debridement that is done can vary markedly. I mean, I think
5 if Dr. Miller's place was involved in it there would be very
6 extensive debridement, while somewhere else there may not
7 be. I think it all depends on who you enlist as to what the
8 outcome is going to be. If you enlist a lot of people that
9 strongly believe and are biased that debridement is going to
10 work, it is going to be very extensive but that may not be
11 what happens in the real world.

12 DR. RELLER: Everyone agrees that debridement is
13 crucial in this process. What I was thinking about in terms
14 of a clinical trial that all would get debridement and you
15 would randomize them to get the vehicle or the vehicle and
16 the active compound.

17 DR. GERDING: My experience when it comes to
18 debridement is that it varies in the extent of debridement.

19 DR. RELLER: That is what randomization is for. I
20 mean, I would like to have them all taken care of by Drs.
21 Lipsky and Miller --

22 DR. GERDING: But I think what that would prove
23 right away is that with very, very aggressive debridement
24 that would happen. You would need to make sure in your trial
25 that you had variations of debridement that are occurring

1 out there and not just get the most extensive ones because
2 if you just got the ones that do the most extensive
3 debridement, then you may be looking at a subset of what is
4 really happening in the real world.

5 DR. RELER: Are you saying that if you get
6 extensive debridement you may not be able to show efficacy
7 and that would deny the drug to those who would get it
8 coupled with inadequate debridement? Where is that going to
9 lead us?

10 DR. GERDING: Well, it is what is happening in the
11 real world as to the extent of debridement. I mean, if you
12 cut away all of the entire infection I think all of us would
13 agree that debridement might be effective. But I am not sure
14 that we do that, and if you are very aggressive, doing it
15 repeatedly, following the patients very closely, I think you
16 probably could show it but I don't think that is what
17 happens in the real world. There are not podiatrists and
18 people out there to see these patients that frequently to be
19 able to do it that way, and often what happens in any
20 clinical trial is that they oftentimes get much better care
21 than they would normally get in their regular practice.

22 So, I think you could design it in such a way that
23 it would end up giving you the answer that you want, no
24 matter what way you want to lead.

25 DR. RELER: I was just thinking that if one

1 doesn't have adequate debridement, then you would want to be
2 very sure that the compound was efficacious. I mean,
3 admittedly there are going to be varying degrees of wound
4 care but it makes it all the more important to know what
5 additional value this or any compound is adding to that
6 wound care, and knowing it with a reasonable degree of
7 certainty so that you could rank them. I mean, as Dr.
8 O'Fallon nicely pointed out, what is a worthwhile increment
9 of good outcome along with what should be done for everyone
10 but may be done to varying degrees of quality?

11 DR. CRAIG: Okay, so we have a placebo trial.
12 Other suggestions of things that should be done? I have
13 already stated that I think the question on wound healing is
14 something that needs to be addressed because, if there was
15 some impairment there, that would nicely explain some of the
16 differences that were observed fm the two trials. Yes, Dr.
17 O'Fallon?

18 DR. O'FALLON: I want to reply to the comment that
19 it would take as big a trial. Actually, to do a superiority
20 trial, which this would be if it were a cream against a
21 placebo, those can be done with fewer patients because you
22 are generally looking for bigger differences. The problem
23 with equivalence is that you are trying to prove that the
24 difference is small. You can usually do it with a smaller
25 trial.

1 DR. CRAIG: Except, I think, our studies within
2 the Division for equivalence are not really true equivalence
3 trials. They do require a smaller number than, I think, if
4 you were trying to really prove true equivalence. I mean, we
5 have given some set variation sizes ahead of time.

6 DR. CHIKAMI: Although, as you recall, this was a
7 topic that was discussed at our advisory committee meeting
8 in July, that in the most recent version of the draft
9 guidances we are, in fact, sort of reassessing those sorts
10 of statements in terms of defining what is a clinically
11 meaningful difference that should be ruled out in a setting
12 of an active control trial.

13 DR. CRAIG: Any other suggestions of things that
14 should be done? Validation of the infection score. Some feel
15 a placebo-controlled trial;, looking at the question of
16 wound healing, effect on wound healing. Anything else that
17 anyone else has to suggest?

18 DR. RODVOLD: In that infection score, I think
19 people were also saying -- and you make it a little simpler
20 than it was, do you need every piece that was currently in
21 it so that it is maybe more user friendly and so people
22 would use it, and can it be modified a little bit or not? I
23 don't know. So, there are two things in there.

24 DR. CRAIG: Okay. Anything else?

25 DR. RELLER: This validation in terms of future

1 things, is validation of a wound score, a usable wound, a
2 necessary ingredient to properly position ultimately this
3 compound for who should receive it?

4 DR. CRAIG: Do we know in the ofloxacin study for
5 which the drug is approved how much debridement was done in
6 that study?

7 DR. CHIKAMI: I would have to go back and look at
8 the review. So, I can't comment on that right now.

9 MR. BOSTWICK: One thing about it, Dr. Craig, is
10 that those are relatively small numbers of patients. There
11 were a number of wound ulcer patients in a larger patient
12 population. I think one of the studies had maybe 60 diabetic
13 wound ulcer patients total, maybe 28 in one group and 30 or
14 40 in the other. So, because it was figured as part of a
15 larger group patients, I don't know exactly how strict they
16 were in debridement and things like that.

17 DR. CRAIG: Okay. Dr. Gerding?

18 DR. GERDING: Just a comment, I think there was
19 probably no restriction on the severity of ulceration or
20 even osteomyelitis in that ofloxacin study, if I guess
21 correctly, so that may be a very different population of
22 patients treated there than what we are talking about here.

23 I would just comment on the wound infection
24 scoring system. It is really a surrogate for how you try to
25 quantitate whether the patient is getting better or not. You

1 know, when you are validating it, what do you validate
2 against? Well, you validate it against all these little
3 incremental changes that take place in each of these
4 variables. I think it would be valuable to look back at the
5 scoring system that has been used and look at each of the
6 variables and see if there aren't some that aren't
7 contributing significantly, i.e., are they always the same
8 in the patients and don't really add anything? Otherwise, I
9 think that scoring system is going to pretty much agree with
10 what the investigator says is happening in terms of response
11 or cure. If it doesn't, then it really is a bad system but
12 everything they showed us would suggest to me that it is
13 going to be valid, and I think it was made up because that
14 is what we think contributes to our gestalt about how a
15 patient is doing. So, other than eliminating useless
16 variables, I don't see that we are going to get a whole lot
17 more out of that wound scoring system.

18 DR. CRAIG: I guess the question that some people
19 were raising was can you use a certain score to identify a
20 subset of patients for which topical therapy would be
21 appropriate, and certain scores for which system therapy
22 would be required to help better define the population. At
23 least, that is what I thought Dr. Norden was trying to bring
24 across with trying to validate it, to use the score as a way
25 of trying to identify which patient population might benefit

1 from using the topical agent.

2 DR. GERDING: Well, to the extent that you might
3 be able to identify failures by a certain score --

4 DR. CRAIG: Right, and that is the other thing,
5 the question where there is a certain score where they fail
6 with treatment with topical therapy, and would that have
7 been an important determinant in this as well.

8 DR. GERDING: The company should be able to tell
9 us that from analyzing their scores, and that should be
10 something they can achieve with their existing data.

11 DR. CRAIG: Yes?

12 DR. HOLROYD: I would just comment briefly that
13 there certainly is a correlation between cured, improved and
14 failed with the clinical response and the wound infection
15 score, for example.

16 DR. CRAIG: So, the higher the score --

17 DR. HOLROYD: The more improvement in the score
18 correlated nicely, I believe, with cured, improved and
19 failed as clinical outcomes, but this addresses more the
20 outcome and not a prospective use of it.

21 DR. LIPSKY: If I may just make one comment, there
22 did not exist any wound infection score and we made this up.

23 DR. CRAIG: Sure.

24 DR. LIPSKY: To my knowledge, no drug that is
25 currently approved for uncomplicated or complicated

1 infection has been asked to meet a standard of a certain
2 wound score. This company, at my urging, went out on a limb
3 to develop a score so that we could have a quantitative
4 ability to say at the end that these patients did or did not
5 get better. So, to say that the wound score wasn't good
6 enough and to hold it to that standard doesn't seem, to me,
7 exactly fair compared to the way other compounds have been
8 looked for the same or similar indication.

9 DR. CRAIG: I think what the committee felt was
10 that it was useful information, at least that is what I
11 remember them telling us, but their only concern was that --
12 you are right -- this is the first time it has been used. Is
13 it also going to prove valuable in others?

14 I think what I am hearing from what appears to be
15 the majority of people, the major concern that they have in
16 terms of the efficacy is how much this was due to the
17 debridement as compared to how much of this was due to the
18 topical agent. At least in my mind, that is the biggest
19 question that the majority of the committee has as to
20 whether there is efficacy.

21 As I said, for the score what Dr. Norden was
22 primarily saying is would this score be useful for including
23 in the package insert some way of identifying that
24 population that would respond well to this form of therapy.

25 Comments or questions? Any questions from the FDA

1 in addition to what we have discussed already?

2 DR. CHIKAMI: No, we have no further questions.

3 DR. CRAIG: Okay, we will be adjourned. Thank you
4 for your time and efforts.

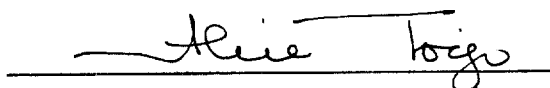
5 [Whereupon, at 4:35 p.m. the proceedings were
6 adjourned.]

7

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C E R T I F I C A T E

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.

A handwritten signature in cursive script that reads "Alice Toigo". The signature is written above a horizontal line.

ALICE TOIGO



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